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WHICH OPERATION FOR CHRONIC DUODENAL ULCER?

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THERE is strong evidence to support the theory that duodenal ulcer is the result of gastric hypersecretion. The two known factors that increase secretion of hydrochloric acid in the stomach are: (1) vagal stimulation from the higher centers, and (2) hormonal stimulation from the mucosa of the gastric antrum. In the patients whose ulcer symptoms cannot be controlled by medical treatment, operation may be necessary. An "ideal" operation for duodenal ulcer, from a physiologic standpoint, would eradicate or neutralize both sources of stimulation. Vagus resection with resection of the antrum theoretically should be the ideal operation if it could be used safely in every patient requiring surgical treatment for ulcer.

Unfortunately, there is as yet no universally applicable operative procedure for chronic duodenal ulcer. Instead, there is a choice of three operations, any one of which may give an excellent result in one patient while failing in another. The surgeon may select from the following:

1. *Subdiaphragmatic vagus resection with posterior gastrojejunostomy* ("Vagotomy with gastroenterostomy").
2. *Subdiaphragmatic vagus resection with conservative gastric resection* ("Vagotomy with hemigastrectomy").
3. *Radical subtotal gastric resection* (Removal of three-fourths or more of the stomach).

There are three potential disadvantages that apply in varying degrees to each of these procedures: (1) risk of operative fatality; (2) recurrent ulceration; (3) disabling postoperative sequellae.

Risk of operative fatality. No surgeon is blind to the importance of calculating risk in operations of election, and, unless the result will justify it, no patient will knowingly submit to an operation that has an appreciably greater risk than the disease for which the operation is being performed. In experienced hands, none of the three operations entails a great risk to life. With *vagotomy with gastroenterostomy* the mortality rate is likely to be less than 1 per cent, but with *radical gastric resection* it is apt to exceed 2 per cent. The proponents of *radical gastric resection* concede that in a small group of patients this operation will be significantly more dangerous than gastroenterostomy. In these patients, where the risk is recognizably higher because of constitutional disease or because of technical problems such as extreme obesity, a poorly taken anesthesia, or an inflammatory mass about the ulcer—will it not be reasonable to perform a *vagotomy with gastroenterostomy*, and avoid a possible

operative fatality at the small cost of reducing slightly the chance of curing the ulcer? The most enthusiastic resectionist will, under such circumstances, occasionally resort to a gastroenterostomy alone, or perform the antral stripping procedure, or the two-stage resection of McKittrick. *Vagotomy with gastroenterostomy* probably in time will replace these other substitutes for a complicated gastric resection.

Recurrent ulceration. It is becoming clear that *radical subtotal gastric resection* gives the patient a high degree of protection against recurrent ulceration, probably in the neighborhood of 98 per cent. Some surgeons have reported an almost equal degree of protection by *vagotomy with gastroenterostomy*, but other surgeons have not been so fortunate. In a series of patients studied at the Cleveland Clinic the incidence of recurrent ulceration after vagotomy with gastroenterostomy rose to 8 per cent in a follow-up study extending beyond three years. This figure is identical with the rate of recurrence in a series of patients treated by conservative (two-thirds) gastric resection performed prior to 1945.

Disabling postoperative sequellae. Although serious nutritional disturbances occurring after operation have been minimized by surgeons who favor removing up to 19/20 of the stomach, the experience of most observers has been that the greater the amount of stomach removed, the greater the likelihood of crippling sequellae. Some patients will tolerate even total gastric resection very well, maintaining their original weight, and eventually reverting to a regimen of three meals a day. But such a response to an extensive resection is exceptional, and most surgeons remove as little of the stomach as they believe to be consistent with a high probability of cure of the ulcer. It may be that the body type of the patient, and his state of nutrition at the time of operation, will offer an accurate index to the amount of stomach which should be removed. Studies by Zollinger suggest that obese patients will tolerate extensive resections without incurring significant loss of weight, while thin or undernourished patients may suffer a further loss in weight after a small resection.

A hopeful compromise between *vagotomy with gastroenterostomy* on the one hand and *radical gastric resection* on the other, is the *vagotomy and hemigastrectomy* advocated by Johnson and Orr in England and by Smithwick in this country. This procedure may prove to be as effective as radical gastric resection in preventing recurrent ulcer, and appears to result in a lower incidence of "gastric cripples."

Some surgeons are restoring intestinal continuity following gastric resection by anastomosing the duodenum directly to the gastric remnant (the Billroth I procedure) in the belief that this operation has a nutritional advantage over the gastrojejunostomy (the Billroth II). Both the incidence and the severity of the dumping syndrome are said to be less with the Billroth I operation, but sufficient time has not yet elapsed to permit a reliable assessment of the results. The cause and the prevention of the dumping syndrome are not yet fully understood, although its incidence appears to increase with an increase in the amount of

gastric tissue removed. Efforts to combat the syndrome by decreasing the size of the gastric stoma have not been fully evaluated.

A study of the pertinent data does not provide a final answer to the question: "Which operation for duodenal ulcer?" Each of the three operations mentioned has strong advocates, and each has implacable opponents. It is possible that additional studies may yet swing opinion one way or another. For example, the observations of Dragstedt indicate that if the gastroenterostomy is placed near the pylorus there is an inhibiting effect on gastric acidity but if it is placed farther from the pylorus it may increase the secretion. This hitherto unsuspected correlation between the position of the gastroenterostomy and the depression of gastric acidity may well account for differences in results reported by various investigators!

In the light of available data, it appears that the operation to be employed in most patients requiring surgery for chronic duodenal ulcer is *vagotomy with hemigastrectomy*. This procedure combines the greatest chance of curing the ulcer, with the least possibility of producing disabling symptoms or nutritional disturbances. When the performance of *any* type of gastric resection, whether extensive or limited, is going to increase the risk to the patient's life, a *vagotomy with gastroenterostomy* may be performed as a less hazardous procedure that still offers a high probability of cure.

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GAUCHER'S DISEASE: CLINICAL FEATURES AND INDICATIONS FOR SPLENECTOMY

Report of 5 Cases

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GAUCHER'S disease is a rare familial disease characterized by the accumulation of the cerebroside, kerasin, in the cells of the reticuloendothelial system. It is classified with Niemann-Pick's and Hand-Schüller-Christian's diseases as a disorder of lipoid storage. The conspicuous clinical feature is extreme splenomegaly with minimal constitutional symptoms, and the diagnosis is established by finding the characteristic Gaucher's cells in the marrow aspirate. Since these cells may be easily overlooked, the marrow examination must be carefully conducted with cognizance of the possibility of their existence. The purpose of this presentation is to describe the clinical features in five cases, selected for their illustrative value, and to discuss the indications for splenectomy.

CASE REPORTS

Case 1. A seven year old Jewish girl was referred to the Clinic in November 1949 because of splenomegaly and hepatomegaly observed during a routine examination one year previously. The child had been a full-term infant and had had the usual childhood diseases. The parents and two siblings were healthy. Extensive studies including marrow aspiration had been performed in 1948, and the results had been reported to be normal with the exception of a mild anemia.

Physical examination on admission disclosed an alert and active child with minimal physical retardation. There was no significant pallor. The spleen was firm and descended to the umbilicus. The liver was 2 cm. below the costal margin. Peripheral lymphadenopathy was absent.

The hemoglobin content of the blood was 13 Gm. per 100 cc. (Haden-Hauser). The erythrocyte count was 4,790,000 per cu. mm. The hematocrit value was 43 cc. per 100 cc. of blood. The leukocyte count was 12,150 per cu. mm. with a normal differential count. The reticulocytes were 1.9 per cent and the icterus index was 4 units. The hypotonic saline fragility was normal. The Wright-stained films showed minimal hypochromia and poikilocytosis. The remainder of the clinical studies including liver function tests and x-ray studies of the gastrointestinal tract were normal. The parents were reluctant to have further marrow aspirations, so the marrow films made one year previously were reviewed and found to be normal.

A provisional diagnosis of Banti's syndrome was made in 1949 and the child was observed at regular intervals. In September 1951, many Gaucher's cells were found in

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a marrow specimen aspirated from the crest of the ilium. A follow-up examination in October 1953 revealed no significant change in the size of the spleen or in the blood counts.

Discussion. The presence of a large, firm spleen associated with hepatomegaly of at least one year's duration in an otherwise healthy Jewish child should suggest the possibility of Gaucher's disease. Banti's syndrome might be considered but such a diagnosis should not be accepted in the absence of other evidence of portal hypertension.

Case 2. A 35 year old Jewish woman had been aware of a large spleen since the age of 18 years when it was detected during her first pregnancy. When first admitted to the Clinic in 1935, the patient had no symptoms except periodic episodes of left upper abdominal pain. The physical examination disclosed mild pallor and a firm spleen extending to the iliac crest. The liver was also firm and extended 5 cm. below the costal margin. The hemoglobin content of the blood was 8.5 Gm. per 100 cc. The erythrocyte count was 3,290,000 per cu. mm. and the hematocrit value was 29 cc. The leukocyte count was 2500 per cu. mm. with a normal differential count. The blood films revealed a moderate decrease of platelets. The reticulocytes were 2.6 per cent and the icterus index was 3 units. A report on this patient had been published by Anderson[1] who had established the diagnosis of Gaucher's disease by splenic aspiration in 1932. One sister of the patient had died at the age of six years with an "enlarged abdomen," another sister had had a splenectomy at the age of seven for Gaucher's disease, and a third sister, 23 years of age, had an "enlarged spleen."

Discussion. It is of interest that the diagnosis in this patient was proved by splenic aspiration in 1932. This procedure was rarely employed at that time but is now generally accepted as a relatively safe procedure in selected patients. Bone marrow aspiration was introduced as a clinical test in 1927[2] but was not in general use in 1932. Today, marrow aspiration is preferred to splenic aspiration to confirm the diagnosis.

The familial occurrence of Gaucher's disease has been reported several times but no specific genetic pattern has been established.

Case 3. A 61 year old Jewish man was first found to have an enlarged spleen during a routine health examination in May 1943. There had been occasional upper abdominal distress which he attributed to daily calisthenics. The physical examination was normal except for the presence of a firm spleen extending 6 cm. below the costal margin, and a palpable liver. The hemoglobin content of the blood was 15 Gm. per 100 cc. The erythrocyte count was 5,340,000 per cu. mm. and the hematocrit value 45 cc. per 100 cc. The leukocyte count was 4350 per cu. mm. with a normal differential count. The icterus index was 6 units. Liver function studies and roentgen examination of the gastrointestinal tract were normal.

The patient was examined again in 1946, at which time the spleen was noted to have enlarged further. The results of hematologic studies including hypotonic saline fragility were within the range of normal and similar to the initial findings three years before. A sternal marrow aspiration was reported as cellular and nondiagnostic. In addition, complete blood studies of the patient's only child were normal.

Progress study in September 1950, seven years after the initial examination, revealed no significant change in the blood count. The spleen now reached the iliac crest. The sternal marrow aspiration was repeated, and a few typical Gaucher's cells were discovered.

In June 1952 the hemogram revealed a hemoglobin value of 11.6 Gm. per 100 cc. The erythrocyte count was 3,960,000 per cu. mm., and the hematocrit reading was 41 cc. The leukocyte count was 2350 per cu. mm. with a normal differential count. The icterus

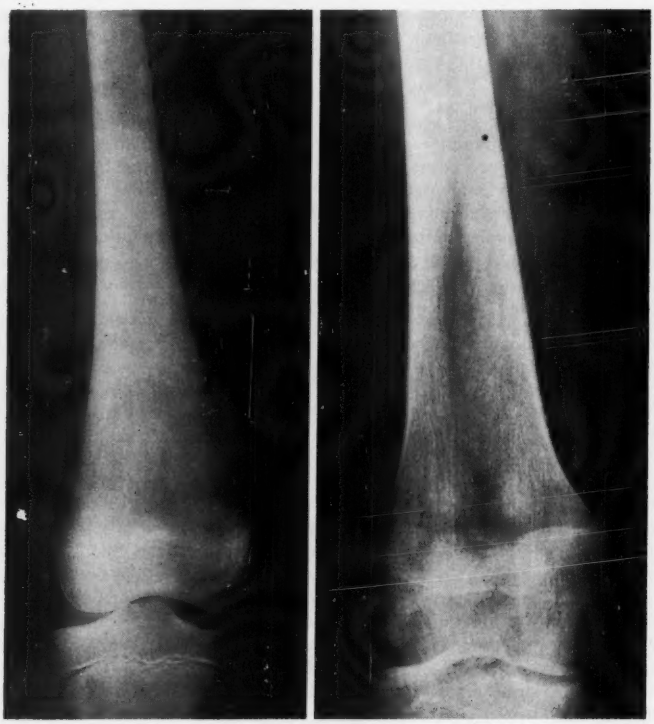
index was 15 units, and the reticulocytes were 4.1 per cent. The platelet count was 60,000 per cu. mm. Bleeding and coagulation times were normal though clot retraction was poor.

The most recent examination in October 1953 disclosed no significant clinical symptoms or change in the hematologic findings.

Discussion. This case illustrates the onset of clinical manifestations of the disease after mid-life. An experienced hematologist failed to recognize Gaucher's cells in the marrow films obtained in 1946. A review of these films, four years later, disclosed the presence of typical cells. This report illustrates how easily the specific Gaucher's cells may be overlooked unless the possibility of their existence is considered and the examination is conducted with extreme care.

It is possible that splenectomy would correct the pancytopenia in this case, but the mild clinical symptoms and the age of the patient make it unwise to advise surgery.

Case 4. A Jewish boy, nine years of age, was first observed in 1950. Splenectomy had been performed in 1947 because of a hemorrhagic diathesis due to thrombocytopenia associated with Gaucher's disease. The operation favorably influenced the hemor-



(a) (b)

Fig. 1. (a) (Case 4) "Erlenmeyer flask" appearance of distal femur in patient having Gaucher's disease. (b) Normal femur for comparison.

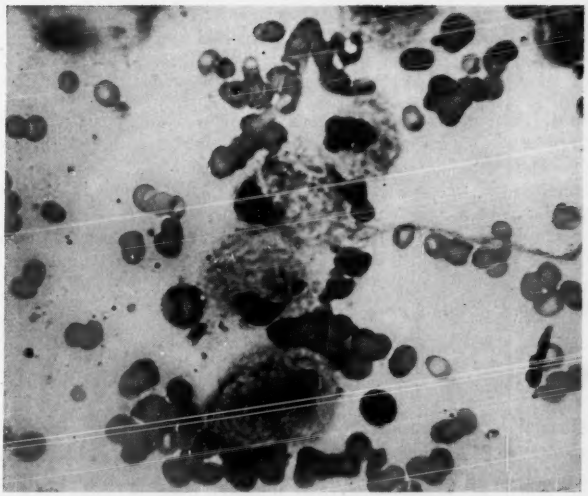


Fig. 2. (Case 5) Gaucher's cells from sternal marrow. Note large size of the cells and "wrinkled tissue-paper" appearance of the cytoplasm. X600.

rhagic state. Dental extractions performed in 1950 were not followed by excessive bleeding. At that time the hemoglobin content of the blood was 11.8 Gm. per 100 cc. The erythrocyte count was 4,140,000 per cu. mm., and the hematocrit value 41 cc. per 100 cc. The leukocyte count was 17,200 per cu. mm. with 33 per cent neutrophilic granulocytes and 67 per cent lymphocytes. The bleeding and coagulation times were normal. X-ray studies of the bone disclosed typical changes observed in Gaucher's disease (fig. 1). In October 1952 the patient was asymptomatic and the examination revealed no significant change.

Discussion. It is apparent that in this patient splenectomy was beneficial in correcting the severity of the hemorrhagic diathesis due to the thrombocytopenia. The slight anemia that persisted may be the result of the marrow replacement by the Gaucher's cells. The osseous lesions demonstrated by roentgenographic examination caused no subjective symptoms. Bone pain and occasionally pathologic fractures may result from infiltration of the bone by the Gaucher's cells.

Case 5. A 39 year old Italian man was referred to the Clinic in July 1953 because of an enlarged spleen first observed during a routine insurance examination several months previously. Diagnostic examinations in his local hospital had failed to establish the cause of the splenic enlargement. The family history was noncontributory. The patient repeatedly stressed the fact that he was feeling well. He participated in active combat duty during World War II without difficulty.

Physical examination revealed an afebrile, well-nourished man. The liver edge was firm and palpable 5 cm. below the costal margin. The spleen was extremely firm and extended 5 cm. below the umbilicus. A sternal marrow aspiration revealed the presence of many typical Gaucher's cells (fig. 2). The hemoglobin content of the blood was 12.0 Gm. per 100 cc. The erythrocyte count was 4,500,000 per cu. mm. The hematocrit value was 41. The leukocyte count was 2600 per cu. mm. with a normal differ-

ential count. The reticulocytes were 3.3 per cent and the icterus index was 9 units. The erythrocytes showed moderate poikilocytosis and anisocytosis. The platelet count was moderately decreased. Roentgen studies disclosed bone lesions in the proximal femurs (fig. 3).

Discussion. The diagnosis of Gaucher's disease was suggested in this case by the benign nature of the marked splenomegaly and was easily established by marrow examination. The possibility of hereditary leptocytosis (Mediterranean anemia) was considered though the spleen was much larger than that usually observed in this condition. If the characteristic Gaucher's cells are scarce, their presence may be overlooked. We wish to emphasize the importance of alerting the hematologist who reviews the marrow films to the possibility of Gaucher's disease so that he will make a careful study of the thicker portion of the films.

There was no indication for recommending splenectomy.

COMMENT

Two clinical pictures of Gaucher's disease have been described. Oberling's[3] infantile type is manifested by a fulminating course with central nervous system involvement. The adult type is characterized by a prolonged chronic course. The disease was formerly believed to occur almost entirely in young persons, but it is now widely recognized that the condition often appears in later life. In Reich's[4] series of 20 patients, 10 were over 40 years of age. Reports[5] have stressed the familial incidence of the disease but no definite genetic pattern of transmission has been established. The disease has been observed in many races, but it most frequently occurs in Jewish people.

The clinical manifestations of the disease are due to the presence of kerasin-filled reticuloendothelial cells in various organs and vary with the degree of infiltration of the organs. The spleen, liver, bone marrow, lymph nodes, kidneys, eyes, central nervous system and other tissues may show infiltration by Gaucher's cells.[6-12]

The cases presented in this report illustrate that the disease may become evident at any age, progress slowly and often cause minimal systemic symptoms. The outstanding feature of the disease is the splenomegaly. In three of the five patients the chance observation of an enlarged spleen eventually led to the correct diagnosis. There are few diseases in a nontropical climate which present splenic enlargement of the degree observed in Gaucher's disease. It is not uncommon for the spleen to descend below the pelvic brim. For clinical purposes the presence of a huge firm spleen should lead the physician to consider Gaucher's disease, myeloid metaplasia of the spleen, chronic leukemia and malignant lymphoma. The liver is also enlarged in Gaucher's disease but to a lesser degree than is the spleen. Skeletal changes due to infiltration with Gaucher's cells are frequently detected on roentgenograms. Though the disease is usually asymptomatic, bone pain does occur and occasionally pathologic fractures are noted.[13] The long bones and those of the pelvis, spine, and skull are most commonly involved.[14] The "Erlenmeyer flask" appearance of the distal femur is considered to be characteristic of Gaucher's disease (fig. 1).

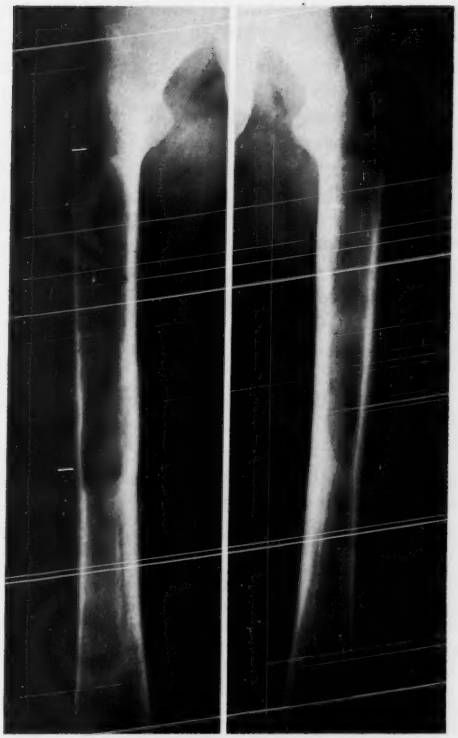


Fig. 3. (Case 5) Bone lesions of femurs in patient having Gaucher's disease.

The patients often show a mild to moderate, normocytic, normochromic anemia depending upon the severity and duration of the disease. Leukopenia is common and is due to granulocytopenia. Thrombocytopenia is frequently observed and may be sufficiently severe to cause purpura, epistaxis, and gingival bleeding. In certain patients the presence of reticulocytosis and the increase of serum bilirubin suggest that the anemia is due in part to excessive hemolysis of erythrocytes. The erythrocyte fragility in hypotonic saline is not altered.

The mechanism of the hematologic changes has not been established. In some patients the infiltration of the marrow by Gaucher's cells may explain the depression of the erythrocytes, granulocytes and thrombocytes. In other patients pancytopenia has been observed in the presence of a hypercellular marrow with minimal infiltration by Gaucher's cells, suggesting that "secondary hypersplenism" plays a major role. It has been recognized for many years

that marked splenomegaly resulting from various diseases may cause a depression of the cellular elements of the peripheral blood.[15]

Although opinions differ as to the indications for splenectomy in Gaucher's disease, there is general agreement that the operation is justified in patients who are experiencing distressing symptoms due to the increased size of the organ. Splenectomy is not warranted as a preventative measure to avoid spontaneous or traumatic rupture, since only one case of traumatic rupture of the spleen in Gaucher's disease has been recorded.[16] There is convincing evidence that splenectomy is beneficial in patients with pancytopenia and a hypercellular marrow if clinical manifestations, such as hemorrhagic diathesis and hemolytic anemia, are present. The mere demonstration of a "secondary hypersplenism" of mild degree by hematologic study does not justify splenectomy. When patients do not obtain clinical or hematologic benefit from splenectomy,[17] the failure to improve is presumably due to irreversible and marked marrow replacement due to Gaucher's cells rather than to hypersplenic effects. Splenectomy does not arrest the progression of the disease because progression of pancytopenia and bone changes have been observed after splenectomy.[10,17,18] Logan[18] cited several instances of patients who survived more than 15 years after splenectomy and included one patient who lived for 31 years after surgery. This report does not prove, however, that splenectomy increases the life span of patients with Gaucher's disease.

SUMMARY

Five reports of patients with Gaucher's disease are presented to illustrate the clinical, hematologic and roentgenologic features of this rare disorder.

The conspicuous clinical feature of this disease is splenomegaly which is out of proportion to the constitutional symptoms. The diagnosis is proved by the demonstration of typical Gaucher's cells in marrow aspirates. These cells may be few in number and may escape detection unless the examiner is alerted to a careful search for them.

There is no specific medical treatment for Gaucher's disease. Splenectomy may be beneficial for distressing mechanical symptoms arising from a large spleen, a hemorrhagic diathesis, or a significant hemolytic anemia.

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SURGERY OF AORTIC ARCH ANOMALIES

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ANOMALIES of the aortic arch represent clinically the most important group of congenital lesions in the heart and great vessels. The clinical importance of these extracardiac anomalies is based on three major factors: (1) accurate diagnosis is possible in most instances, (2) surgical correction is possible in the majority of cases, and (3) definitive surgical therapy may offer a normal life expectancy to the patients.

Aortic arch anomalies are classified in the noncyanotic category of congenital heart disease. In a high percentage of cases early recognition of the condition is possible during infancy and preschool childhood. Most important, it is in this group of congenital lesions that surgery offers a physiologic cure if intervention occurs before irreversible secondary changes have become manifest. In contrast, surgery for intracardiac lesions is usually of a palliative nature in congenital heart disease and should not be considered curative except in isolated instances.

PATENT DUCTUS ARTERIOSUS

Persistence of the ductus arteriosus occurs more frequently than any of the other aortic anomalies. In 1939 Gross[1] reported the first successful ductus ligation; this brilliant surgical feat provided a tremendous stimulation to clinical interest. Ductus surgery is commonplace today, attesting to the importance of Gross' contribution.

The ductus arteriosus is an integral part of the fetal circulation; with the foramen ovale it shunts most of the blood flow from the right side of the heart and the pulmonary artery into the systemic circulation. Functional closure occurs shortly after birth and eventual obliteration is represented by the ligamentum arteriosum.[2]

When patency persists, there is a great alteration in circulatory dynamics. Aeration of the lungs at birth is associated with a fall in pulmonary vascular resistance and a relative decrease in pulmonary arterial pressure. During the first months of life, pressures in the systemic circulation progressively exceed the pulmonary arterial pressure. At the beginning there is an appreciable differential only in systole, and a reversal of the fetal shunt occurs with systolic aorto-pulmonary flow. This early phase of patent ductus arteriosus may persist

during the first two to four years of life and manifest itself by only a systolic murmur. With body growth the resistance in the systemic circulation increases until aortic diastolic pressure greatly exceeds the diastolic pressure in the pulmonary artery. When this occurs the shunt continues from aorta to pulmonary artery throughout all phases of the cardiac cycle and the characteristic continuous murmur appears (fig. 1). When the continuous, or "machinery,"

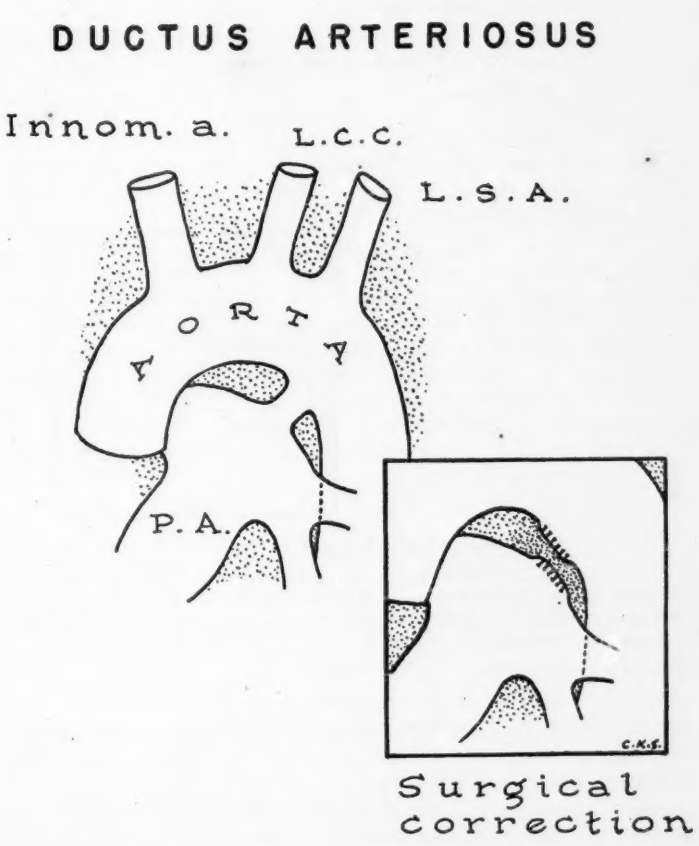

Fig. 1. The patent ductus arteriosus is a direct communication between the descending arch of the aorta and the pulmonary artery; as such it shunts arterial blood from the aorta into the "venous" blood of the pulmonary arterial circulation. In effect, this is a physiologic arteriovenous shunt. Surgical treatment must offer permanent obliteration of this shunt; surgical division, rather than ligation in continuity, best accomplishes this end.

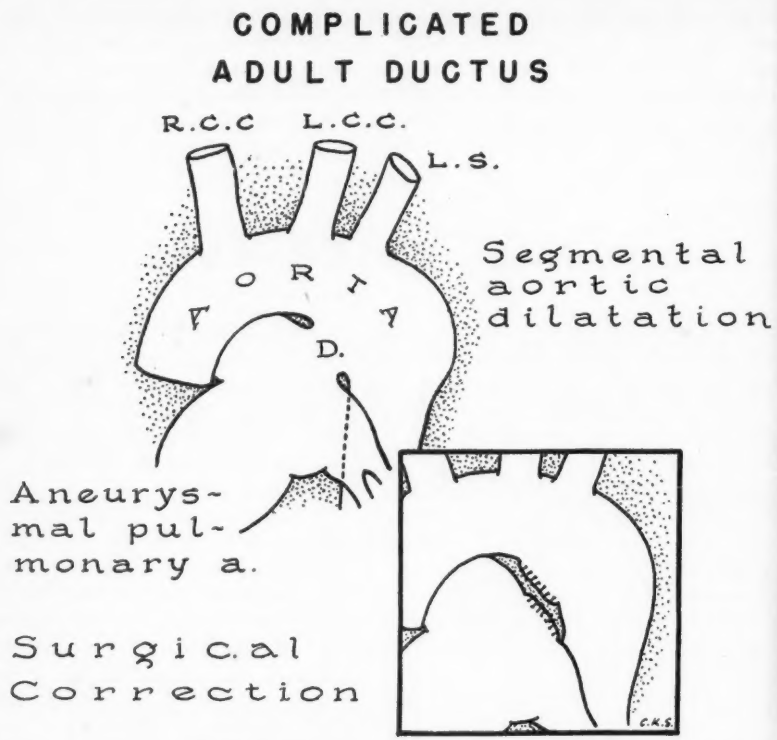

Fig. 2. Complicated ductus arteriosus with aneurysmal changes is usually observed in young adults. Dilatation of the aorta at the level of the ductus may be associated with medial necrosis of the aortic os. Aneurysm of the pulmonary artery effects both shortening and widening of the ductus. In all probability this is the "window" type of ductus described by Rokitansky[6] in 1852. Surgical division of the complicated ductus will be facilitated by controlled arterial hypotension.[3,7,8]

murmur is present it is usually diagnostic of a patent ductus arteriosus, nevertheless a significant feature must be recognized—the absence of a continuous murmur does not indicate the absence of a patent ductus arteriosus! We have treated ten infants between 4 and 33 months of age, who suffered severe cardiac embarrassment because of large ducti producing only a systolic murmur. In each case it was possible to demonstrate the lesion by cardiac catheterization and to effect surgical obliteration of the shunt. We believe that the majority of these infants would have died before a continuous murmur were to become apparent.

Adults with patent ductus arteriosus who develop progressive pulmonary

hypertension and degenerative changes in the pulmonary artery lose the continuous murmur, if pulmonary arterial pressure rises to systemic levels; in this group, the continuous murmur may give way to a systolic murmur only. Occasionally a "to-and-fro" murmur may be present because of the development of pulmonary valve incompetence; in such a case the clinical picture may closely resemble that of aortic insufficiency. Cyanosis is never a clinical feature of patent ductus arteriosus, unless accompanied by another lesion (fig. 2).

The treatment of patent ductus arteriosus is surgical. Division of the ductus is the ideal therapy and is superior to ligation in continuity. Operative mortality in patients with uncomplicated ductus arteriosus is less than 2 per cent. The ideal candidate is the youngster of 5 or 6 years who demonstrates only the typical auscultatory findings of the anomaly. In such a patient the lesion should be corrected when it is recognized, before bacterial endarteritis, myocardial insufficiency, pulmonary aneurysm or other local vascular changes occur, as these complications add appreciably to the surgical risk. We have found controlled arterial hypotension to be a valuable adjunct in surgical division of complicated ductus arteriosus. When there is aneurysmal dilatation of the pulmonary artery or local degenerative changes in the aorta or ductus, the risk of uncontrollable hemorrhage is considerable. These degenerative changes may be secondary to previous infection or simply to progressive, long-standing pulmonary hypertension. However, when these changes are present, the elasticity and the integrity of the involved vessel walls are greatly altered. Reduction of the intraluminal pressure by controlled arterial hypotension facilitates the dissection of the complicated ductus and adds appreciably to the safety of the operation. Intra-arterial transfusion is an effective means of treating surgical hemorrhage should it occur in spite of all precautions.[3]

COARCTATION OF THE AORTA

Coarctation is a localized constriction of the aorta; in the adult form the constriction is at or below the ligamentum arteriosum. The constriction may be total, producing complete obstruction. More commonly it presents a small, eccentrically placed lumen that permits a jet-like stream of blood to enter the distal aorta. The constant impingement of this jet stream against the wall of the descending aorta may produce a localized atheroma (jet plaque) and predispose to a localized aneurysm.

Coarctation of the aorta produces a radical alteration in the circulatory dynamics. Obstruction below the ligamentum ductus produces the pathognomonic findings of hypertension in the upper extremities and a corresponding hypotension in the lower extremities (fig. 3). The blood volume through the constricted area may be negligible or absent. Hence, a well-developed collateral circulation is necessary to supply the trunk and lower extremities. Three main pathways develop: (1) the internal mammary arteries supplying the anterior chest wall and abdomen enter the inferior epigastric arteries; (2) the high intercostals

convey blood from the first branches of the subclavian arteries to the aorta below the constriction; and (3) the descending vessels in the scapular area arise from the subclavian and axillary arteries to supply the posterior chest wall and communicate with the perforating branches of the lower intercostals. It is the development of these tortuous collaterals which produces the visible pulsating vessels in the interscapular region and the characteristic rib notches visible on the roentgenogram.

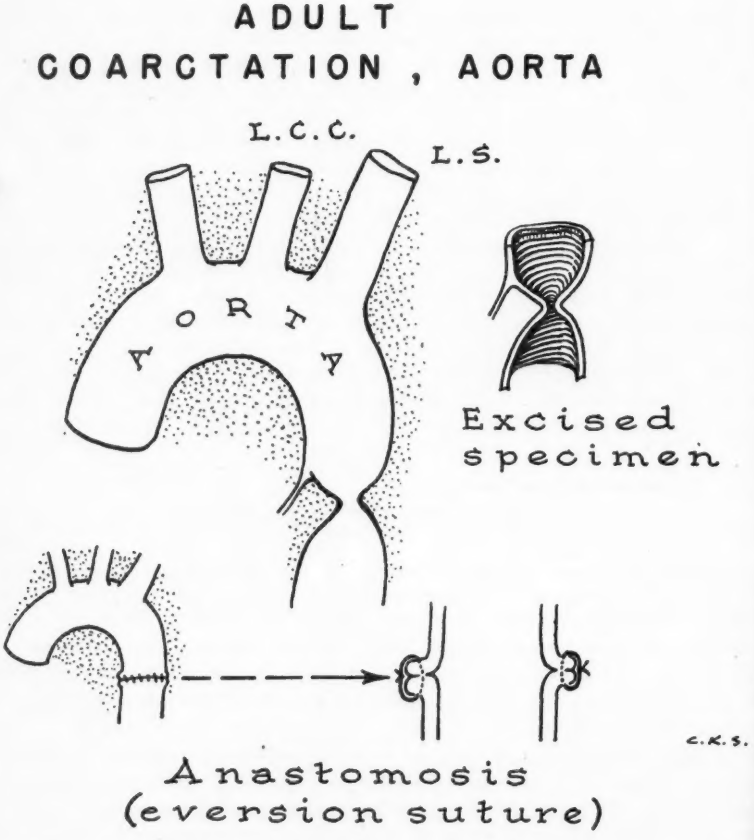

Fig. 3. Simple type of adult coarctation occurring below the ligamentum arteriosum. The localized constriction may have a tiny lumen or complete diaphragm. Surgical correction is accomplished by excision of the constricting lesion and primary end-to-end anastomosis of the aortic segments.

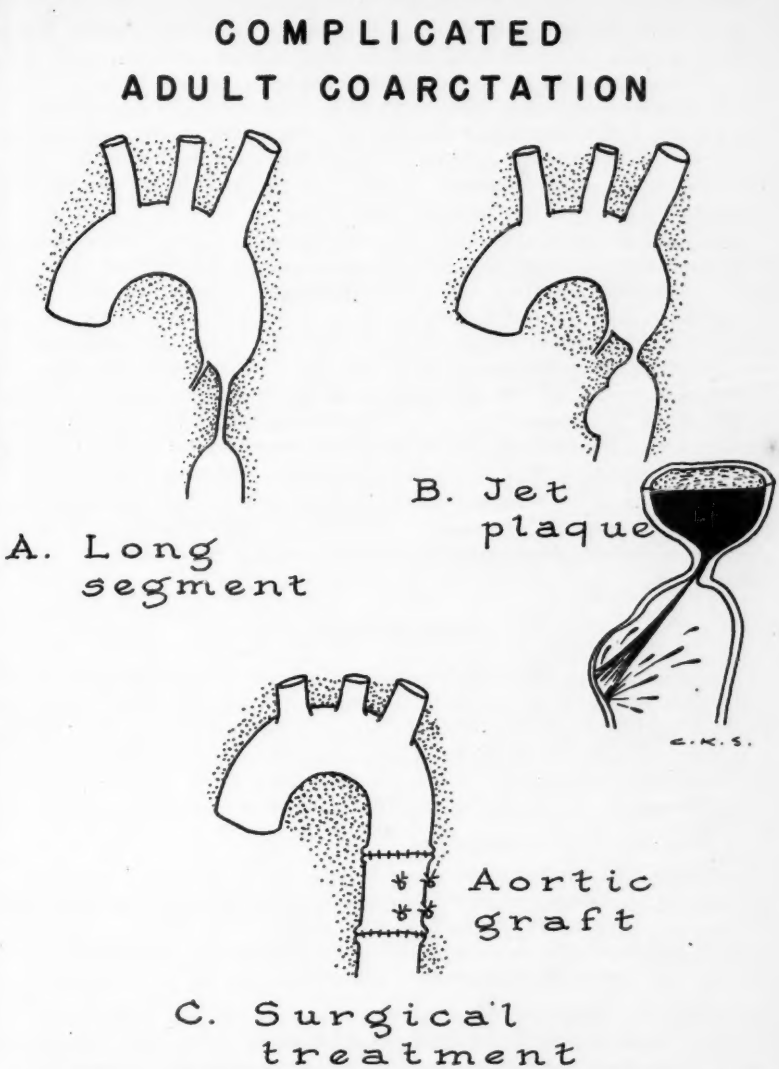

Fig. 4. A. Occasionally the area of constriction is several centimeters in length. Excision of this type of coarctation will not permit primary approximation of the aortic segments. Preserved aortic graft is used to bridge such a gap. B. Simple coarctation with an eccentric, intraluminary ring may direct the jet-like stream against the wall of the descending aorta. A localized atheroma (jet plaque) may develop at this point; localized aneurysm below the coarctation will require more extensive resection than described in figure 3.

The dangers of untreated coarctation are widely known. In addition to the obvious hazards of severe hypertension with cardiac embarrassment and cerebral vascular accident, patients with untreated coarctation may develop medial necrosis of the aorta with dissecting aneurysm or spontaneous rupture. It is our belief that the vascular degeneration of untreated coarctation appears earlier in young men and may be a serious factor by the age of 20 years. Recognition and surgical therapy in patients between 5 and 10 years of age approximates the ideal treatment for this condition.

The surgical treatment of adult coarctation is best accomplished by excision of the constricting lesion with end-to-end anastomosis of the proximal and distal aortic segments.[4] Less direct methods that utilize the dilated subclavian artery to bypass or re-establish continuity of the aorta are falling into discard. If the area of constriction is unusually long, or there are irreversible degenerative changes in the aorta immediately above or below the coarctation, arterial grafts should be employed (fig. 4). Medial necrosis of the proximal aorta, or in the region of the jet plaque below, is a serious threat to anastomotic healing; dissecting aneurysm or frank dehiscence of the suture line has occurred days or weeks after operation when this localized vascular degeneration was present.

Coarctation of the aorta is a serious anomaly which when untreated has a poor, over-all prognosis. Recognition and proper surgical intervention before the onset of vascular degeneration and cardiac embarrassment offer a promising outlook.

AORTIC RINGS

The third major group of arch anomalies includes the so-called aortic rings. These developmental anomalies of the aortic arch and its major vessels are characterized by reduplication of the arch, by anomalous origin of a major tributary, or by deviation of the normal left-sided pattern to the right. In a previous communication[5] devoted to the diagnosis and the treatment of aortic rings, we suggested the following simple classifications of these anomalies:

Group I—Left Descending Aorta:

(a) Left aortic arch (normal adult).

(b) Left aortic arch with right subclavian artery arising on descending aorta distal to the left subclavian artery (dysphagia lusoria).

(c) Left aortic arch (with or without atresia) and a functioning right arch constituting an anatomic double arch.

Group II—Right Descending Aorta:

(a) Right arch (mirror image of normal aorta).

(b) Right arch with dysphagia lusoria (mirror image of b in Group I).

(c) Right aortic arch with a functioning left arch (mirror image of c in Group I).

This group of embryologic anomalies, aortic rings, possesses a clinical significance that should not be overlooked. The term ring is employed because

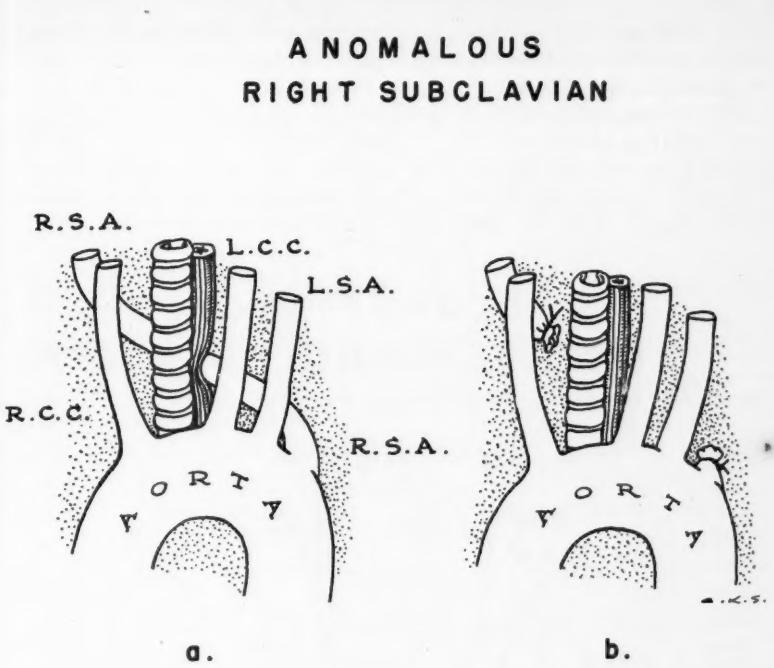

Fig. 5. a. Simple aortic rings produced by retro-esophageal, right, subclavian artery which arises from the descending aorta below the normal left subclavian artery (after Gross).[9] b. Obstruction of esophagus (dysphagia lusoria) relieved by surgical division of the anomalous right subclavian artery. Division of this vessel does not impair the arterial circulation of the right arm.

each of these variations results in a vascular encirclement of trachea, of esophagus, or of both tubes (fig. 5). If the encirclement is tight enough to encroach upon these hollow tubes, mechanical impairment will result. Usually the anomaly itself produces no embarrassment in circulation; it is the constriction of the trachea and/or of the esophagus which produces disease.

Symptoms produced by aortic rings will usually appear in infancy. The degree of severity is usually proportional to the degree of mechanical encroachment of the encircling vessel on the esophagus or trachea. Some children will have obvious distress in respiration or in feeding, and even at rest; others will manifest these symptoms only during stress imposed by physical exertion or secondary infection. Unusual feeding problems characterized by prompt regurgitation and choking spells may suggest a vascular anomaly. Likewise, persistent wheezing and stridor may be due to extrinsic tracheal compression;

when these respiratory symptoms are coupled with a mechanical feeding problem, the possibility of a vascular ring is very real (fig. 6).

Methods of diagnosis have been described in detail[5] and will not be repeated here. It is worthwhile to state, however, that clinical suspicion and simple radiographic studies may serve to establish the presence of a ring. The exact nature of the anomaly can be determined by retrograde arteriography in a large percentage of cases. Proper diagnostic studies will have a great influence on the surgical result, since each of the lesions is amenable to surgical relief.

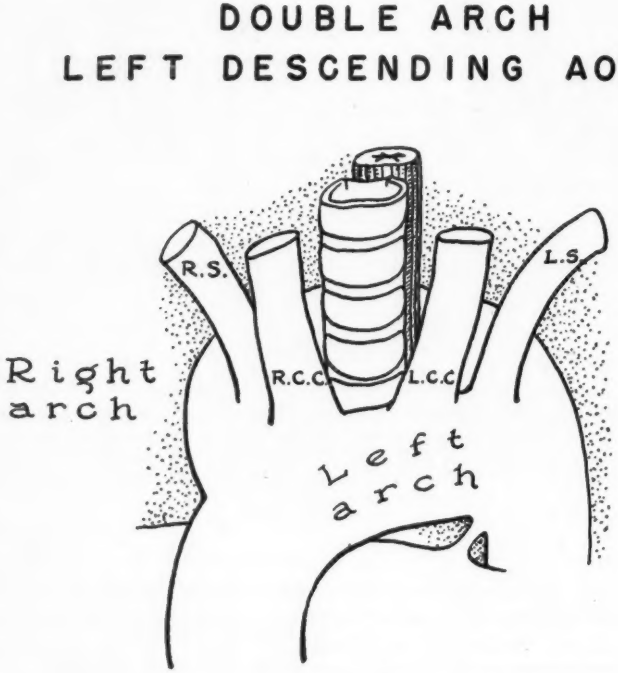

Fig. 6. Double aortic arch with left descending aorta (after Gross).[9] In this case both arches are patent; surgical division of the left arch to relieve tracheo-esophageal compression may be done with comparative safety.

SUMMARY

Anomalies of the aortic arch do not produce cyanosis unless accompanied by other cardiac lesions or as a terminal feature of cardiac failure. Recognition of

these lesions is mandatory if surgical correction is to be accompanied by a low mortality figure. Most of these congenital abnormalities present clinical features that are recognizable on physical examination alone; diagnostic refinements, such as cardiac catheterization and aortography, are necessary in a comparatively small percentage of cases.

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HYALURONIDASE AS AN AID TO CORRECTION OF PARAPHIMOSIS

Report of a Case

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PARAPHIMOSIS is a condition in which the prepuce becomes displaced and fixed behind the glans penis. It is often painful. It is almost invariably associated with a tight preputial margin that acts as a constricting ring when it retracts behind the glans; this often occurs during sexual intercourse. The constriction soon creates a "doughnut-like" ring of edema interposed between the constricting band and the glans penis which prevents replacement of the prepuce to its normal position covering the glans.

In those few patients who are seen before the edema becomes too extensive, it is possible to replace the prepuce by manually compressing the edema and then "rolling" the prepuce over the collar of edema. When this is unsuccessful, we have heretofore had to resort to surgical correction by means of a dorsal slit which divides the constricting preputial band.

Williams and Nichols[1] in 1952 reported the use of hyaluronidase in reducing paraphimosis in three patients; more recently my attention was drawn to this useful procedure by Ratliff[2] who reported a case similarly treated. I have recently utilized this method of treatment in one patient and the result was most gratifying. This case is described here in order to disseminate information regarding this useful procedure; it is hoped this may benefit others who may be called upon to treat those afflicted with this benign though painful condition.

CASE REPORT

A man, 23 years of age, was referred to me because of a painful swelling of the penis. Examination revealed a typical paraphimosis which was stated to be of almost 48 hours' duration. There was some bleeding as a result of earlier vigorous attempts to reduce the paraphimosis. The pain produced by these attempts had made the patient apprehensive.

One hundred and fifty turbidity reducing units of hyaluronidase was dissolved in 2 cc. of a 1 per cent procaine solution and then drawn into a syringe. After the skin of the penis was cleansed, the constricting ring of the prepuce was exposed by gently retracting the edematous collar. Through a No. 23 needle, ½ cc. of the hyaluronidase-procaine solution was injected into the ring (favoring the distal, edematous side) at the top, at the bottom, and on each side (fig. 1). Distribution of the solution was aided by placing an annular band of gauze and then gently massaging the injected solution into the tissues.

Within 15 minutes the tense, edematous "doughnut" had noticeably softened and,

in 20 minutes, it was possible to express the remaining edema fluid into the adjacent tissues. The prepuce was then painlessly replaced to its normal position with the greatest ease. The patient was advised to return at a later date for circumcision.

COMMENT

The rationale and success of this method of treatment are based upon a peculiar property of hyaluronidase. This enzyme acts by depolymerizing the long chains of polymerized hyaluronic acid which constitute the bulk of the ground substance of connective tissue. This ground substance normally limits the spread of fluids and other extracellular material. By unmeshing its weave, hyaluronidase permits local accumulations of fluid to spread farther and more

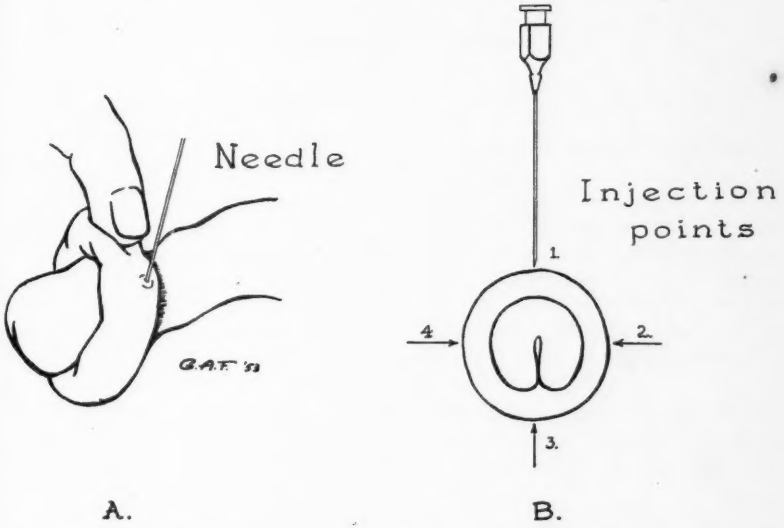

Fig. 1. (A) Drawing showing edematous tissue being rolled forward to expose constricting ring. Injection made just distal to the constricting ring. (B) Diagrammatic representation of points of injection.

rapidly, and thus promotes their absorption. This action was dramatically demonstrated in this case. No doubt this property of the enzyme hyaluronidase can be extended to many other situations in which it is useful to dispel tense edema fluid quickly from the tissue. I believe that the dilution of the hyaluronidase in a procaine solution offers a distinct advantage in that it combines the hydrolyzing effects of the enzyme with the local anesthesia provided by the procaine solution.

SUMMARY

A case is reported in which a painful paraphimosis of two days' duration was successfully, easily, and painlessly reduced by the use of hyaluronidase dissolved in a 1 per cent procaine solution injected into the edematous and constricting ring.

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A SURGICAL APPROACH TO CERVICAL CARCINOMA

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CERVICAL CARCINOMA may be treated by surgery or by irradiation therapy. The two forms of treatment should be thought of as being complementary rather than competitive. In considering surgical therapy, a middle-of-the-road approach seems most reasonable in the light of present knowledge.

Indications for Surgery

The treatment of choice in the majority of cases of cervical carcinoma is irradiation therapy since 70 to 75 per cent of women with this disease have evidence of its extension outside the cervix when they are first examined. It follows then that surgery is most commonly indicated in those cases in which there is a failure of response to irradiation therapy. Surgery may also be employed for the following purposes: (1) evaluation of response of a lesion to previous irradiation therapy; (2) palliation; (3) correction of conditions arising out of the use of x-ray or radium therapy; (4) complete pretreatment evaluation when undetermined extracervical pelvic pathology coexists with a Stage I or Stage II cervical carcinoma; and (5) treatment of carefully selected cases of Stage I and Stage II cervical carcinomas; these operations are being performed in some centers by highly competent surgeons.

It has been suggested that surgery be routinely advised upon a patient's refusal to accept irradiation, but we believe that a patient cannot reasonably make a choice between therapeutic procedures which in most instances must be decided by the surgeon.

Contraindications to Operation

Contraindications to surgery are difficult to outline, for often surgical exploration itself is essential to complete evaluation of a given condition. A neoplasm that upon bimanual examination appears to be hopelessly advanced may upon surgical exploration prove to be operable. Age of the patient is of less importance in determining operative risk than is physiologic condition. Edema of the legs of pelvic origin, and leg and deep pelvic pain nearly always indicate a hopeless condition. Obesity in a patient who has a deep, narrow pelvis may make a thorough operation impossible. Certainly extrapelvic metastases render local therapy useless.

Failure of Irradiation

It is generally possible to determine the response of the local lesion to irradiation treatment not only by the examination of smears and of biopsy specimens obtained during and after therapy, but by clinical appraisal. The presence or absence of tumor cells in cervical and vaginal smears is not important. The important changes to look for in nonmalignant cells are vacuolization of cytoplasm, increase in cell size, and nuclear atypism which, as pointed out by Graham,[1] indicate susceptibility of the carcinoma to irradiation therapy. If irradiation is given and, at the conclusion of treatment, such changes are not found or actively growing cancer is demonstrated clinically or by biopsy, surgical intervention is indicated.

The advancing growth of cancer in extracervical locations is more difficult to evaluate. Following extensive irradiation, fibrosis of irradiation areas often occurs, making it impossible to differentiate between changes that result from carcinomatous extension and those from irradiation. By close follow-up examination it is generally possible to detect progressive changes. Everett, Brack and Farber[2] and Aldridge and Mason[3] have pointed out that progressive ureteral obstruction is often due to advancing carcinoma; consequently, before any irradiation therapy is given, urographic studies should be carried out, and following the completion of irradiation they should be repeated at frequent intervals.

Second-Look Operations

General surgeons for the past several years have been performing so-called "second-look" operations six months to a year after an initial surgical procedure. The status of the abdomen can thus be evaluated with surety, and occasionally this provides another opportunity for palliative therapy, or, very rarely, curative therapy. Today, simple exploration involves an almost negligible risk; the risk being largely associated with anesthesia.

In cases of gynecologic carcinomas in which reasonable doubt exists in regard to the response to initial x-ray and radium treatment, surgical exploration permits the determination of the lateral and upward extent of the tumor and may make it possible to carry out surgical therapy before the lesion becomes so far advanced as to make such therapy impossible. Intra-abdominal excisional biopsies are invaluable in conjunction with such a procedure, but biopsy specimens must be reliably diagnosed by frozen section technics. Explorations of this type should be carried out only if the surgeon, the patient, and the operating room are prepared for a possible, immediate, extensive, definitive operation.

One of the effects of x-ray and radium therapy which is often underemphasized is the entrapment of carcinomatous cells by fibrous connective tissue. Thus, undue manipulation should be avoided in any secondary operation. If resectable carcinoma is found, it would seem wise to remove the uterus and

adnexal areas in addition to carrying out a lymphadenectomy in order to avoid possible reactivation of dormant, controlled carcinoma in these areas.

Radical Approach to Extensive Recurrent Disease

The possible surgical procedures for treatment of recurrent or persistent carcinoma range from radical hysterectomy to total pelvic exenteration and are so varied that few surgeons have sufficient experience to handle them all with equal facility. This creates a problem that we have met by using the combined talents and skills of all specialists concerned. Thus, the choice of treatment and the actual operations may represent the cooperative efforts of several specialists. If a procedure involves the urinary and gastrointestinal tracts as well as the reproductive organs, a urologist, a general surgeon, and a gynecologist collaborate, each performing the particular part of the operation which is within his special field. The patient's well-being is not sacrificed by any limitation of surgical ability, and each part of the operation is performed with maximum dispatch by a surgeon not fatigued by prolonged operating. The patient's postoperative course is followed by all doctors concerned, and their efforts and interests are coordinated by one resident. We have done 12 combined procedures involving partial or complete pelvic exenteration with transplantation of the ureters without an operative or hospital mortality. At present it is too early to evaluate these operations accurately, but rapidly increasing evidence indicates that this type of surgery may constitute a very definite contribution to the treatment of otherwise hopeless lesions.

Surgery for Irradiation Sequellae and Palliation

Surgery may be employed in dealing with the sequellae of irradiation, or may be used for palliation. Urinary tract conditions in which surgery is employed include intractable irradiation lesions of the bladder with severe hematuria, vesicovaginal or ureterovaginal fistulas and ureteral obstruction. Closure of fistulas and diversionary operations even in hopeless cases where prognoses are limited will simplify nursing care and considerably increase the comfort of the patients. In the case of hopelessly advanced neoplasm, it would seem unwise to attempt to relieve ureteral obstruction, but when obstruction exists with controlled or controllable neoplasm, operative intervention may be lifesaving, since some patients die of bilateral ureteral obstruction with no extrapelvic spread of their disease.

Fistulous communications may exist between the gastrointestinal tract and the vagina, and may be rectovaginal or enterovaginal communications—secondary to neoplasm or irradiation. A permanent colostomy is generally indicated in rectal strictures. Secondary pull-through operations (resection of the area of stricture with re-anastomosis of the sigmoid to the rectum or anus) can be considered, but scarring usually is so extensive that this is impracticable. With such a procedure, cancer cells entrapped by fibrous connective tissue may

also be set free. However, when colostomy is performed for the postirradiation type of rectovaginal fistula, a secondary closure of the fistula may be possible later. This operation should not be considered until sufficient time has elapsed following primary therapy to indicate that recurrence of the carcinoma is unlikely.

An enterovaginal fistula may be treated by a so-called short-circuiting operation. The segment of bowel involved in the fistula is excluded from the main stream of intestinal contents but is allowed to remain in situ. We have recently performed such an operation on each of two patients in whom fistulas were due to carcinoma, not to irradiation, and though their prognoses were limited and hopeless, we believe that the procedure was fully justified in that it simplified nursing care and made the patients much more comfortable.

Operations for the relief of intractable pain include cordotomy and lobotomy; a life expectancy of at least four to six months is desirable before carrying out these procedures. These operations often complicate nursing care, as temporary urinary incontinence occurs regularly in all cases of bilateral cordotomy and is persistent in about 10 per cent. In general, narcotics have been used liberally and further palliative x-ray therapy has been attempted in lieu of these operations. Procaine injections into the frontal lobes have been introduced too recently to evaluate.

On several occasions in an attempt to relieve deep pelvic pain, we have placed low-intensity radium needles in metastatic carcinoma at the time of abdominal exploration. There is considerable sloughing of necrotic tissue following this procedure, and although the patient may obtain relief from pain, intestinal fistulas may result. This complication has led to the abandonment of this form of therapy.

Summary

Irradiation therapy and surgery are complementary forms of treatment in cases of cervical carcinoma. Surgery may be employed either for curative or for palliative purposes. For best results in individual cases, the full cooperation of the various surgical specialists and the radiologists is necessary. Greatest progress can be made only by centralizing the cases, by cooperative group attack, and by individualizing therapy.

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THE USE OF CORTISONE IN THE TREATMENT OF THE PANHYPOPITUITARISM DUE TO POSTPARTUM NECROSIS OF THE PITUITARY (SHEEHAN'S SYNDROME)

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IN a series of articles, the first of which was published in 1914, Simmonds[1-3] described destruction of the anterior lobe of the pituitary gland and its clinical effects. This condition became known as Simmonds' disease.

Knowledge of this disease has been greatly broadened by the work of Sheehan,[4,5] who, in 1937, first described areas of pituitary infarction and fibrosis due to thrombosis with necrosis occurring in women having a history of severe postpartum hemorrhage accompanied by shock and usually coma. The anterior pituitary failure which results from this type of lesion is usually, but not always, more extensive than that produced by other types of lesions of the pituitary. If the gonadotropins, thyrotropin and corticotropin are all absent, the condition is termed "panhypopituitarism," despite the fact that the function of the posterior lobe is not known to be unimpaired. If the secretion of only one or two of these hormones is deficient, the condition may be termed "selective" or "partial" pituitary failure.

Thus, the symptoms and signs of the panhypopituitarism of Sheehan's syndrome are largely due to the effects of secondary atrophy and failure of the adrenal cortices, the thyroid and the ovaries. Most of these symptoms, signs and laboratory findings are described in the following two case studies.

The main purpose of this paper is to discuss the use of cortisone or hydrocortisone in the treatment of the adrenal cortical failure that occurs secondary to severe anterior pituitary failure.

CASE REPORTS

Case 1. A 33 year old white woman was first seen here in October 1937. Six years prior to admission she had had a severe postpartum hemorrhage with shock requiring packing of the uterus during an otherwise normal delivery. This was her first pregnancy. She was unable to nurse her baby and developed permanent amenorrhea. Her energy and endurance decreased and she lost 10 pounds in weight during the next two years.

Her skin became dry and her axillary and pubic hair became scanty. There was no appreciable change in sexual libido.

Physical examination revealed her height to be 63 inches, and weight 115 pounds. Her blood pressure was 100/70 mm. Hg. The skin was dry. The pubic hair was sparse and the axillary hair was almost absent. There was some loss of hair from the eyebrows. The external genitalia were normal. The uterus was atrophic and the vaginal wall was devoid of rugae. There was no excessive pigmentation of the skin.

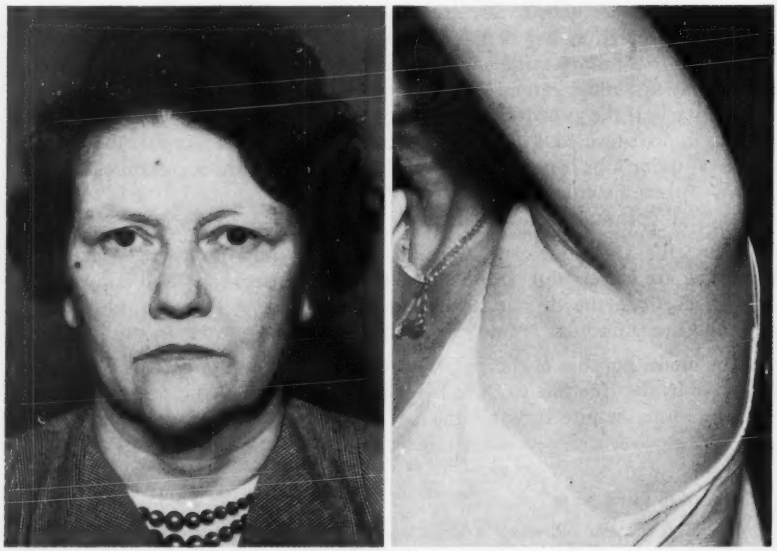
Laboratory examination revealed the following: X-ray of the sella turcica was normal. The basal metabolic rate was minus 20 per cent. Urinalysis was negative. The red blood cell count was 4,340,000, the hemoglobin was 78 per cent, and the white blood cell count was 5650. The blood sugar was 92 mg. per 100 cc. 3¾ hours post cibum.

A diagnosis of anterior pituitary deficiency was made.

Therapy with 1½ gr. desiccated thyroid per day and 200 U. APL three times weekly was initiated. However, although the patient felt some initial improvement, response could not be accurately evaluated because she discontinued the medication and contact with her was lost.

Fourteen years later in October 1951, the patient was readmitted with the same complaints; sexual libido had now disappeared.

Physical findings were substantially the same as on her previous visit. Her weight was 124 pounds and the blood pressure was 108/74. Photographs of the patient taken at this time are shown in figure 1.



(a) (b)

Fig. 1. (Case 1) Sheehan's syndrome with mild adrenal cortical failure. (a) Facies essentially normal except for pallor. (b) Left axilla demonstrating loss of axillary hair.

The serum sodium and serum potassium levels were 133 and 4.8 mEq/L., respectively. The plasma cholesterol was 328 mg. per 100 cc. Fasting blood sugar was 97 mg. per 100 cc., and a single dose, oral, glucose tolerance test showed the following: fasting 97 mg., one-half hour 126 mg., one hour 122 mg., two hours 119 mg., three hours 77 mg., and four hours 111 mg. per 100 cc. The basal metabolic rate was minus 24 per cent. Adrenalin and ACTH tests revealed a fall of 35 and 54 per cent, respectively, of eosinophils in the blood at the end of four hours. Original counts were 72 and 156, respectively. Urinary gonadotropins were more than 6 but less than 13 m.u. per 24 hours. The urinary 17-ketosteroids were 0.7 mg. per 24 hours. The vaginal smear was castrate in type and the uterus was atrophic. The uterine canal was 5 cm. in length. The endometrium was so atrophic that no material could be obtained for biopsy.

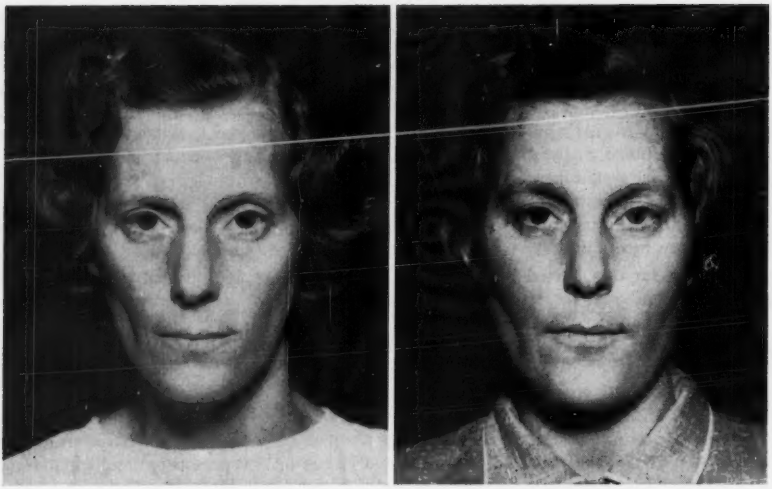
The patient was started on oral cortisone, 50 mg. per day divided into four doses, and she was advised to return in four weeks to receive desiccated thyroid and testosterone. Although her condition improved at the beginning of cortisone treatment, she soon experienced a sense of nervous stimulation and irritability that caused her to discontinue the therapy. She described herself as being "all keyed-up" while taking the drugs, and did not return for the thyroid and androgen treatment. When she returned one and a half years later, an I^{131} test revealed an uptake of 10 per cent in 24 hours. The plasma cholesterol was 387 mg. per 100 cc. The basal metabolic rate was minus 34 per cent. A dose of 12.5 mg. a day of cortisone was prescribed and the patient noted marked improvement in strength and appetite. Her skin was still dry and pale, and her nails were somewhat brittle. Blood pressure was 110/82. Therapy with cortisone was continued and she was given 1 gr. of U.S.P. desiccated thyroid daily. Three months later, her plasma cholesterol was 232 mg. per 100 cc. Ten mg. of testosterone (buccal) was administered twice a day. On her return three months later, she reported that she felt entirely normal for the first time in 20 years. Her sexual libido had returned to normal. There was some light hair on the chin and cheeks. Her weight was 135 pounds. The blood pressure was 130/82; the plasma cholesterol was 226 mg. per 100 cc.; and the basal metabolic rate remained low, being minus 27 per cent.

Case 2. A 33 year old white woman was first examined here on August 4, 1953. She was chiefly concerned in regard to extreme weakness, oligomenorrhea, a weight loss of 18 pounds and episodes of coma.

Her history revealed that in 1943, after her second child was delivered, she had a severe uterine hemorrhage followed by profound shock. She recovered with the aid of blood transfusions without any residual effects, except that during the next three years she noted weakness and a loss of weight from 140 to 120 pounds. Her menstrual periods continued to be regular; they had always been scanty and lasted three days. In 1945, she had her third child. Two days after arriving home, the patient again had a uterine hemorrhage, but in this instance it was not followed by shock.

In 1951, six years after the birth of her third child, the patient first noted the onset of oligomenorrhea; during this year she had only four menses, in 1952 she had two, and in 1953 she had two scanty menses for three days each in April and August.

In June 1951 during an episode of migraine headache associated with vomiting, the patient lapsed into a coma which lasted three days from which she recovered spontaneously. In May 1953 during another episode of migraine associated with vomiting, the patient again lapsed into coma for two days. Two blood samples obtained during this episode were found to have blood sugar contents of 16 and 32 mg. per 100 cc., respectively. The patient was promptly revived by only the intravenous administration of glucose. Three weeks prior to her initial examination here a third episode of hypoglycemic coma relieved by glucose occurred which again followed migraine headache



(a) (b)

Fig. 2. (Case 2) Sheehan's syndrome with severe adrenal cortical failure. (a) Typical facies demonstrating apathy, pallor and weight loss prior to treatment. (b) Essentially normal facies following three months of treatment with cortisone, desiccated thyroid and estrogen.

associated with vomiting. She had experienced neither nausea nor vomiting during the time between the episodes of hypoglycemic coma. Because of a poor appetite her weight had decreased 18 pounds during the two years preceding the examination. Her weakness had become so extreme that she was unable to do any of her housework.

Treatment of the patient's condition had consisted of 1 gr. of desiccated thyroid taken daily for the two years prior to admission and injections of ACTH three times a week for a few weeks prior to admission. No estrogen had been prescribed.

Physical examination revealed her weight to be 102 pounds and her height to be 62 inches. The systolic blood pressure was 90 mm. Hg, but diastolic pressure could not be recorded in the sitting position. The patient was apathetic, pale and listless. Axillary hair was absent and pubic hair was scant. Pelvic examination disclosed no evidence of a pathologic condition or genital atrophy. There was some melanosis over the forehead and sides of the face which the patient said had been present for the past year. She had noticed the same condition during each pregnancy but it had disappeared after each delivery. There was no increased pigmentation elsewhere on her body.

Laboratory studies revealed a flat glucose tolerance curve with hypoglycemia. The blood sugar levels were as follows: fasting 62 mg., one hour 77 mg., two hours 50 mg., three hours 48 mg., and four hours 42 mg. per 100 cc. No insulin tolerance test was done in view of the obvious hypoglycemia. The first part of the Robinson-Kepler-Power test showed an overnight urine volume of 645 cc., and the largest hourly volume after ingestion of 20 cc. of water per Kg. of body weight was 35 cc. The Kepler index was 0.4. The ACTH test was normal with a 60 per cent fall in eosinophils from 200 to 81. Blood studies revealed the sodium to be 129 mEq., potassium 3.8 mEq., carbon dioxide 26.1 mEq., and chlorides 99 mEq. per liter; the serum calcium was 10.5 mg., phosphorus

3.5 mg., and cholesterol 205 mg. per 100 cc. A differential white blood cell count showed 41 per cent neutrophils, 7 per cent eosinophils, and 52 per cent lymphocytes. The basal metabolic rate was minus 38 per cent. The 24-hour urinary 17-ketosteroid value was .2 mg. (normal, 5 to 9 mg.). There were no corticoids found in a 24-hour urine specimen (method of Reddy, Jenkins and Thorn[6]). The hemoglobin content was 13.4 Gm. X-ray of the sella turcica was normal. Microscopic examination of two specimens of urine, including one catheterized specimen, revealed marked pyuria. A vaginal smear was loaded with pus and trichomonads.

Treatment consisted of the simultaneous administration of 50 mg. of cortisone, 1 gr. of U.S.P. desiccated thyroid every day and 1 mg. of stilbesterol daily for 25 of each 30 days. Small doses of testosterone or methyltestosterone may be added to the therapy program in the future if necessary. While the patient was taking cortisone, the blood sugar levels before each meal were 62 mg., 64 mg., and 111 mg. per 100 cc. The patient was not given feedings between meals, She was advised to use salt liberally but not excessively in her food.

On November 7, 1953, the patient returned saying that she felt completely well for the first time since 1943. She was more alert, her appetite was good, and she had gained 18 pounds in weight. She was able to do all of her housework with ease. Her sexual libido had returned. The hypoglycemic attacks had not recurred. Her axillary hair was beginning to return. There was no edema of the legs. On her face, the pallor had disappeared and the melanosis (chloasma) had almost completely disappeared. Figure 2 includes photographs of the patient before and after therapy.

Laboratory study at this time showed a basal metabolic rate of minus 20 per cent, fasting blood sugar of 80 mg. per 100 cc., plasma cholesterol of 235 mg. per 100 cc., and a differential white blood cell count of 61 per cent neutrophils, 2 per cent eosinophils, and 37 per cent lymphocytes.

DISCUSSION

These two patients with panhypopituitarism presented quantitive and qualitative differences in the manifestations of their disease. While the first patient developed amenorrhea following the onset of pituitary failure and never menstruated again, the second patient continued to menstruate regularly every month for eight years after the episode of necrosis of the pituitary gland. Oligomenorrhea occurred in the second patient two years before admission, but the menses, though rare, did not cease. Also, she was capable of becoming pregnant two years after the first episode of postpartum hemorrhage, indicating that, although pituitary failure already existed as evidenced by the presence of weakness and weight loss, ovarian function was still adequate. This is not an uncommon occurrence in this type of pituitary failure. Sheehan[5] states that permanent amenorrhea occurs in the most severe cases only, while in the less severe cases the menses may persist for a few months to several years and then stop. In others the menses may return completely to normal.

There were no characteristic physical findings that indicated that either one of these patients was truly myxedematous, i.e., swollen puffy face and delayed reflexes, but there were changes that suggested that they might have mild hypothyroidism.

The adrenal cortical failure in case 2 was much more marked than that in case 1, as evidenced by the second patient's (case 2) apathy, severe weakness, extreme weight loss and episodes of hypoglycemic coma relieved by the intravenous administration of glucose. This type of hypoglycemic coma without electrolytic changes should be distinguished from acute adrenal cortical failure or adrenal crisis which is usually evidenced by electrolyte changes with or without hypoglycemia. The former may be relieved by intravenous glucose alone, while the latter will require, in addition, replacement adrenal cortical therapy. The organic hypoglycemic episodes in the second patient were precipitated by migraine headaches associated with vomiting; the headache and vomiting caused an inadequate intake of food which resulted in a blood sugar content so low that coma occurred. The intravenous administration of glucose alone promptly revived her from her comatose state. The hypoglycemia in the second patient may be due both to a deficiency of growth hormone that has an anti-insulin effect and to a deficiency of ACTH that helps to maintain the blood sugar level by stimulating the adrenal cortices.

In treating adrenal cortical failure, the physician must decide whether to use physiologic stimulative therapy with ACTH, or replacement therapy with cortisone (Compound E) or hydrocortisone (Compound F). Cook, Bean, Franklin and Embrick,[7] Schrock, Sheets and Bean,[8] and Summers and Sheehan[9] have noted that patients with this syndrome respond much more satisfactorily to cortisone than they do to ACTH. Knowlton, Jailer, Hamilton and West[10] also have noted a poor response to ACTH in their patients. These authors[7-10] believe that the presence of long-standing adrenal cortical atrophy is the reason for the unsatisfactory response to ACTH. Furthermore, Summers and Sheehan[9] noted the occurrence of hemiparesis in two patients who received 25 mg. of ACTH every eight hours. The paresis disappeared after treatment was discontinued. Schrock, Sheets and Bean[8] noted the development of toxic psychosis in their patient treated with 25 mg. of ACTH every six hours. It is likely that doses of ACTH, not excessive under other circumstances, may have been excessive in these cases[7-10] and were responsible for the striking untoward symptoms. Heyde[11] noted that his patient with Sheehan's syndrome, who responded rapidly to ACTH, developed insomnia on 15 mg. of ACTH a day which disappeared when the same dose was given every other day. In contrast to the previous reports, he noted that 10 mg. of corticotropin gel every third day and 2.5 mg. of desoxycorticosterone every day plus other glandular replacement therapy were sufficient to maintain the patient in good health. Maddock, Leach, Klein and Myers[12] noted that the administration of 10 to 20 mg. of ACTH every six hours produced a good response in four men with selective pituitary failure and marked secondary adrenal cortical failure. However, this response did not occur until the third day of administration. In addition, they noted that 25 mg. of ACTH a day maintained these patients satisfactorily.

Therefore, while the adrenal cortex in some patients with panhypopituitarism may respond to ACTH, the experience quoted has shown that consist-

ently good results cannot be predicted. In addition, those who do respond may have a delayed response which is also a disadvantage particularly if one has to treat a patient in adrenal crisis. Thus, it is our belief that cortisone or hydrocortisone is to be preferred instead of ACTH. That cortisone may produce a rapid as well as effective response is substantiated by Abbott and Simmons[13] who reported that their patient with Sheehan's syndrome in adrenal crisis responded in 24 hours to 200 mg. of cortisone. For continuous therapy it is particularly advantageous that cortisone is active when administered orally.

It is important that the dose of cortisone be individualized. The first patient (case 1) felt so stimulated and uncomfortable that she was unwilling to continue taking 50 mg. of cortisone daily which was originally prescribed. When the dose was reduced to 12.5 mg. per day she noted a great symptomatic improvement and the disappearance of the stimulation. On the other hand, the second patient (case 2) did well on 50 mg. of cortisone a day and experienced no toxic symptoms. The rather marked hypoglycemia was corrected by this dosage. Skillern and Rynearson[14] and Steiner[15] have also noted that cortisone is most beneficial in controlling the hypoglycemia of pituitary failure. It should be stressed to the patient that if she is unable to take cortisone by mouth due to illness, she should inform her doctor immediately so that he can give her the needed cortisone intramuscularly. The dose should be increased for the duration of the illness.

Cortisone seems to be beneficial not only to patients with clinical adrenal cortical failure such as that which is present in Sheehan's syndrome, but also in the type of adrenal deficiency which may occur secondary to other types of pituitary lesions. However, we would like to emphasize that many patients, especially men, with certain types of pituitary failure, such as that seen postoperatively or in the presence of sellar, suprasellar or parasellar, space-taking lesions of various sorts, may be improved greatly by testosterone alone. In fact, some, who have not only severe gonadal deficiency but readily measurable evidence of adrenal defect as well, may evidence so much improvement on testosterone alone that the addition of cortisone scarcely seems to be needed. In some patients we have observed that the addition of cortisone causes little or no further symptomatic response and is not worth continuing.[16] However, if patients such as these are subjected to any severe stress it may be wise to use cortisone.

Hydrocortisone may be used instead of cortisone. The properties of this drug have been reviewed recently by Thorn and his associates.[17] The metabolic effects of hydrocortisone are qualitatively similar to those of cortisone. The main difference is that hydrocortisone is about twice as potent as cortisone milligram for milligram; therefore, the dose of hydrocortisone should be about one half of the estimated dose of cortisone. The only disadvantage of hydrocortisone is that it is ineffective when administered intramuscularly, being effective only when it is given orally. This drug is now available and offers one advantage over cortisone in that it is less likely to produce central nervous system stimulation to which these patients and those with Addison's disease

seem peculiarly susceptible, sometimes even when small average maintenance doses are given.

We believe that a regular diet without frequent feeding is sufficient in these patients. We advise the patient to use salt liberally on his food, but we do not prescribe any extra salt. If the patient requires less than 50 mg. of cortisone a day it may be necessary to prescribe 2 to 4 mg. of desoxycorticosterone (linguets) a day, if the blood pressure remains low, symptoms of weakness persist and electrolytes in the blood remain low after a few weeks of treatment.

Since no good anterior pituitary extract is readily available, other replacement hormone therapy is also necessary in severe cases such as the two we have presented. If an adequate dose of cortisone is prescribed, there is no reason why 1 gr. of uncoated U.S.P. desiccated thyroid cannot be started simultaneously since the danger of precipitating adrenal crisis has been eliminated. Schrock, Sheets and Bean[8] noted that a patient with Sheehan's disease developed obvious myxedema when given cortisone alone which was corrected by adding desiccated thyroid. These same authors[8] noted that in the presence of adrenal cortical deficiency the administration of desiccated thyroid precipitated adrenal crisis when cortisone was withheld. Means, Hertz and Lerman[18] and Perkins and Rynearson[19] have emphasized the danger of giving desiccated thyroid alone to patients having severe pituitary failure such as usually is seen in Sheehan's syndrome.

In the premenopausal woman (before the age of 45 years) it is also advisable to recommend estrogen replacement therapy, such as stilbesterol 1 mg. a day 25 of each 30 days. Since the normal androgens are almost totally missing from the body, it is logical that some androgen be given. For this, methyltestosterone may be administered as sublingual tablets in a dose of 10 mg. or more per day. This will help to maintain a normal protein balance, will restore normal sexual libido, and will assist in the normal regrowth of axillary and pubic hair.

The transformation of the condition of such patients as these from that of chronic invalidism before treatment to one of essentially normal health following therapy is most striking and gratifying. There is no doubt in our minds that cortisone was chiefly responsible for the improvement in the two patients whose case reports we have presented here.

SUMMARY

The clinical features and laboratory findings in two cases of panhypopituitarism due to postpartum necrosis of the pituitary gland have been presented. Multiple glandular replacement therapy, particularly cortisone, transformed the state of these women from one of chronic ill health to one of essentially normal health. In our second patient, cortisone not only relieved the systemic effects of adrenal insufficiency but also corrected a severe hypoglycemia. The use of cortisone or hydrocortisone in preference to ACTH is advocated because they are more surely effective, more rapidly effective, and more easily administered.

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ROENTGENOGRAPHIC DIAGNOSIS OF ACOUSTIC NERVE TUMOR

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THE diagnosis of acoustic nerve tumor is based primarily upon the results of clinical examination; roentgenographic examination serves as a secondary diagnostic aid. This lesion is not uncommon, constituting approximately 9 per cent of all brain tumors.

The tumor is found attached to the eighth cranial nerve and lies in the angle between the cerebellum and the brain stem. The direction of growth is variable; a tumor may grow quite large without appreciably involving the petrous apex or extending into the acustic meatus. By contrast, it may weigh only a few grams with most of its mass within the meatus, causing marked erosion. Although initially it was postulated that the tumor arose solely from the vestibular branch,[1] now it is known that either the vestibular or the cochlear branch of the eighth nerve may be the site of origin.[2] Acoustic nerve tumors have been reported in the literature to be of two basic histologic types.[3] Most of them are considered to be neurinomas (neurilemoma, perineural fibroblastoma); in these, the nerve fibers are confined to the capsule of the tumor mass with no fibers present within the lesion. A small percentage are neurofibromas with nerve fibrils coursing through the tumor. The latter are reported as occurring with von Recklinghausen's disease;[4] they tend to be bilateral and familial,[5] and may be associated with a meningioma.[6,7] All of the acoustic tumors in this series were reported as neurilemomas or neurinomas, including two cases with von Recklinghausen's neurofibromatosis peripherally. It seems definite that there is an increased incidence of acoustic tumor in cases of neurofibromatosis. However, tissue from these central lesions apparently shows no significant histologic differences from that of any other acoustic nerve tumor.[8]

Although there are exceptions, symptoms tend to divide themselves into three phases.[9] These in general reflect the increase in size of the lesion. In the first phase, there is local involvement of the eighth nerve, followed by involvement of the fifth and seventh cranial nerves. In the second phase, with further tumor growth, the cerebellum and the ninth, tenth, and eleventh cranial nerves are also involved. Symptoms of increased intracranial pressure due to blockage of the aqueduct of Sylvius occur late, and represent the final phase.

In a considerable proportion of cases no definite changes are apparent on roentgenographic examination, plain films of the skull being entirely negative

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or showing such minimal variation in the petrous apices and acustic meati that they are within the range of normal. In detecting those cases with roentgenographically demonstrable lesions, close scrutiny is required because the changes are usually inconspicuous. Diminished bony density around the meatus caused by local erosion with a sharp line of demarcation between the involved area and normal bone may be the only findings (fig. 2). Extensive bony destruction with a gross defect in the petrous apex occurs in only the minority of cases (fig. 4). The reported accuracy of diagnosis by roentgenographic examination varies considerably. Dyke[10] states that about 50 per cent of cases will have sufficient demineralization and erosion to be visible on roentgenograms; this appears to be a reasonable average. Percentages as high as 84 and 90 have been reported by Hodes, Pendergrass and Young,[11] and by Lysholm.[12]

SERIES

The purpose of this article is to review the roentgenographic evidence in those surgically proved cases of acoustic nerve tumor which were observed at the Cleveland Clinic from 1946 to 1952. Of 43 such cases during this period, films were available for study in 36. In most of these 36 cases a tentative diagnosis of acoustic neuroma had been made prior to the time of roentgenographic examination. In the remainder, some type of posterior fossa growth was under consideration. Seventy-five per cent of the patients were women (27 women and 9 men). The lesion was located on the right in 19 cases and on the left in 16. The only instance of bilateral acoustic tumor in this series occurred in a 20 year old woman who had had von Recklinghausen's disease since early childhood. She had, in addition, a sphenoid ridge meningioma. The average age on admission was 46 years. Four of the patients, all women, were in their twenties and the oldest patient was 70 years of age. These figures are in general agreement with those reported for other larger series by Cushing[4] and Gonzales Revilla;[8] that is, the tumor is more common in women, and more patients present themselves for surgery in their early forties than at any other age.

A routine series of roentgenograms of the skull which consisted of stereoscopic right laterals, posterior-anterior, and occipital views were obtained of all patients. Of the 36, 24 had in addition a basilar view, and 22 had a Stenver's view. The changes observed on plain films can be divided into two main categories: (1) local changes in the petrous bone in the region of the lesion, and (2) nonspecific changes due to increased intracranial pressure. Since pneumoencephalographic studies of this condition are uncommon and rarely necessary for diagnosis, they will not be discussed.

In attempting to evaluate changes in the petrous bone, three major groups were used. In the *first group* were those cases in which definite erosion and loss of bony substance was demonstrated: these findings were considered positive. In the *second group* were those cases showing changes suggestive of a local lesion. Although these findings were consistent with an acoustic tumor, an

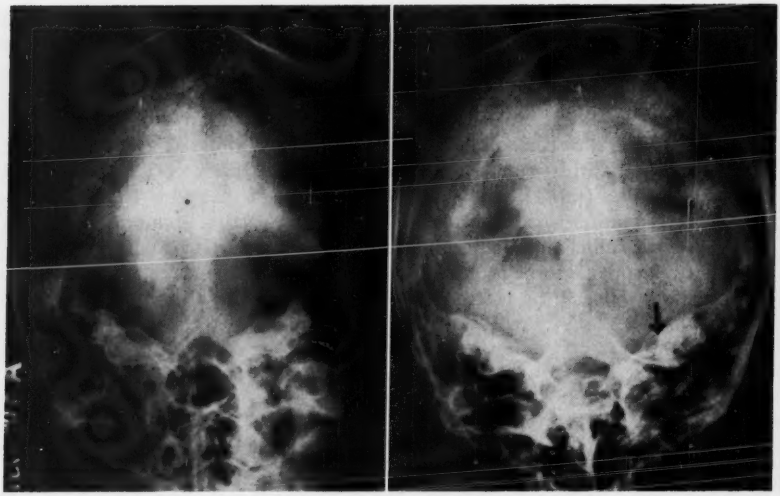

Fig. 1 Fig. 2

Fig. 1. Normal occipital view. The acustic meati are clearly visible.

Fig. 2. (Woman, 25 years of age) Left acoustic neurilemoma. There is minimal erosion about the acustic meatus. The arrow points to the sharp line of demarcation between the involved area and normal bone.

unequivocal diagnosis was believed to be unwarranted. Included in this group were those cases in which roentgenograms showed slight density changes that apparently represented bony involvement, but conceivably could have been caused by projection or by normal asymmetry. Also included were suspicious differences in the size of the acustic meati without definite erosion evident on roentgenograms. Camp and Cilley[13] have shown in a careful study that there is considerable variation in the size and shape of the normal acustic meati with the normal diameter ranging from 2.5 to 11 mm. Differences up to 2.5 mm. between the two sides of the same patient were seen. The *third group* consisted of those cases with roentgenographic findings considered to be within normal limits.

It is distinguishing between minimal pathologic change and the wide range of normal that affords the greatest difficulty. A point is reached at which one can reasonably justify the presence of a known lesion on the basis of minimal changes; yet almost identical findings can be reproduced in a normal case. This fact we believe explains in large part the wide variation in accuracy of roentgenographic diagnoses reported in the literature. However, another important consideration is the excellence of roentgenographic technic including the use of stereoscopic views in various positions.

In this series, findings were positive (group 1) in 11 cases, suggestive (group 2) in 10, and within normal limits (group 3) in 15. Thus in 21 (58 per cent) of

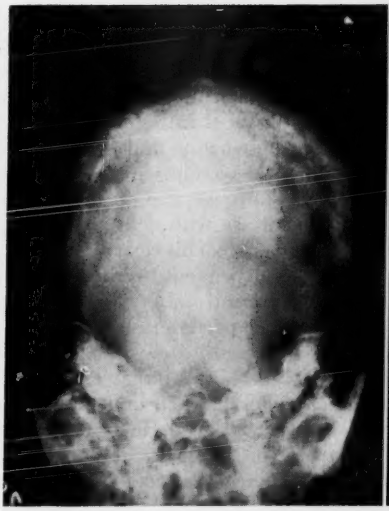

Fig. 3

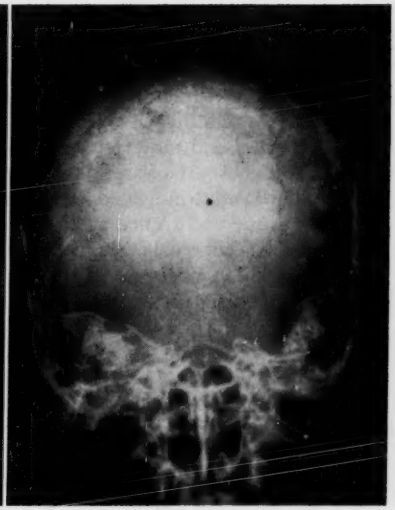

Fig. 4

Fig. 3. (Man, 41 years of age) Left acoustic neurilemoma. Erosion of moderate degree is present in the region of the acustic meatus.

Fig. 4. (Woman, 59 years of age) Left acoustic neurilemoma. There is unusually marked erosion with destruction of the entire petrous apex.

36 cases, the roentgenologic evidence was adequate to support the diagnosis of acoustic tumor. Evidence obtained from all views has been incorporated into this total impression since, except in the most advanced cases, findings vary according to the projection utilized. By far the most valuable view was the occipital (Towne) view, in which the petrous ridge is thrown free of superimposed structures and its superior-posterior surface visualized. Changes were demonstrated on this view in all of the positive group and in three instances it was the only film to show erosion. Acoustic tumor was suspected on this view in eight of the ten cases in the second group; in one of the two with negative findings, projection was not entirely satisfactory.

Second in value to the Towne view was the basilar view. It showed the clearest evidence of bone destruction in 2 of the 11 cases in group 1. In the second group, the basilar view showed changes on the two occasions when the Towne view was negative. In no case was the Stenver's view most informative and changes could be seen in only a small percentage of cases. The posterior-anterior view was of little or no value in this series since, as routinely made at the Clinic, the petrous ridges are superimposed over the maxillary bones. If special positioning is used with the petrous bone projected through the orbit, this view can be of considerable value. Some investigators, including Camp and Cilley,[13] consider it superior to the Towne.

As mentioned previously, increased intracranial pressure tends to occur late in this disease, and it is most commonly manifested on plain films by changes of the sella turcica. These include straightening of the posterior clinoids with demineralization or actual erosion, and occasionally enlargement of the sella turcica. These findings in contrast to the local changes in the petrous bone are nonspecific, and may result from ventricular obstruction and dilatation of any cause. Of the 21 cases in groups 1 and 2, there were 4 with a definitely abnormal sella that indicated increased intracranial pressure. Of considerable interest was the occurrence of a ballooned sella turcica with definite thinning of the posterior clinoids, observed in one case in group 3. This clearly illustrates that the variation in roentgenographic findings is dependent on the direction of tumor growth. In this case the lesion was apparently able to grow large enough free in the cerebellopontine angle to produce partial obstruction without causing sufficient involvement of the petrous bone to show on roentgenographic examination. In general, however, it would appear that changes in the petrous bone and sella turcica tend to be parallel, since four of the five cases in which change occurred in the sella turcica were all in the first group with definite petrous erosion. No definite abnormality of the sella was seen in the second group. There were several cases of slight demineralization of the posterior clinoids in all three groups which may have represented early increased intracranial pressure but which fell within the range of normal variation.

To correlate the size of the growth with the incidence of change in the petrous ridge is difficult because the actual size of the lesion cannot be determined from its weight at removal, since a variable portion of mass may be cystic and the tumor is usually removed piecemeal. However, as might be expected, there was no particular relationship apparent and of the four largest tumors, all heavier than 20 Gm., only two were in the first group. The duration of symptoms prior to surgery was also considered to determine whether there were a relationship between length of time the lesion was present and the roentgenographic findings. The total number of cases did not allow for any statistical conclusions with the average for the first group 4.1 years, for the second group 2.9 years, and for the third group 3.3 years. However, whereas of the 15 patients in the negative group only 3 had symptoms 5 years or longer, of the 11 in the positive group 5 had symptoms of this duration. These findings suggest that in cases in which the patient's symptoms have been of long duration, there is greater likelihood that changes can be demonstrated on roentgenographic examination.

SUMMARY

1. The diagnosis of acoustic nerve tumor is chiefly clinical.

2. Changes, when observed on plain roentgenograms, result either from local involvement of the petrous bone, or from nonspecific changes that are due to increased intracranial pressure.

3. In 58 per cent of the cases in this series, there was adequate roentgenologic evidence to support the diagnosis of an acoustic lesion; that is, 21 of the 36 cases showed changes in the petrous bone.

4. The Towne view was found to be the single, most valuable projection.

5. Although cases with abnormality of the sella turcica caused by increased intracranial pressure usually also demonstrate local change, such abnormality can be seen in the presence of a normal petrous apex.

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CHANGING CONCEPTS OF ANESTHESIA DEPTH

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GUEDAL'S[1] description of the planes of surgical anesthesia with ether has led to the wide use of his chart in interpreting the depth of surgical anesthesia. Surgical anesthesia is, in these terms, characterized by unconsciousness, insensitivity to pain, moderate muscular relaxation and impairment of certain reflexes; indeed, loss of the eyelid, the swallowing and the vomiting reflexes is indicative of passage from the second to the third stage.[2] As new anesthetic agents have come into use, notably thiopental sodium, it has been determined that it is both dangerous and impossible to define surgical anesthesia in general in terms of the stages practical with ether.[3] Such an interpretation however is still implicit in most publications, so that many clinicians believe that an adequate anesthetic level is not obtained until the patient is totally unconscious and unresponsive to external stimuli. Such levels of "surgical anesthesia" may be dangerous; they are sometimes associated with serious cardiac arrhythmias, and circulatory and respiratory depressions.

The gas-oxygen-ether (GOE) of yesterday has largely given way to an anesthesia accomplished by the judicious combination of several agents, each of which performs its special function. It is therefore necessary to examine and to re-evaluate the planes of anesthesia and to identify their components.

The benefits of light anesthesia were described in 1914 by Crile[4] when he outlined his theory of anoci-association. If local anesthetic is used to block all painful somatic stimuli originating at the site of the surgical incision, and light cortical suppression is accomplished with another anesthetic agent, the patient is protected against the noxious peripheral and psychic stimuli associated with operation. Using the agents of his day, Crile accomplished this by combining procaine infiltration of the operative field with general anesthesia by nitrous oxide. By the judicious administration of nitrous oxide, a very light plane of anesthesia may be maintained. This has been described as the stage of analgesia.

COMPONENTS OF SURGICAL ANESTHESIA

The necessary components of surgical anesthesia are (1) *hypnosis*, (2) *analgesia*, and (3) *relaxation*. Certain undesirable side effects, such as depression of circulation and irritation of the respiratory tract, may accompany surgical anesthesia, especially if an agent such as ether is used to furnish all of the components. When different agents are combined, each of which safely provides one component, the side effects and long reaction time of deep ether anesthesia are avoided. As here described the three components are respectively provided by thiopental, nitrous oxide, and a muscle relaxant. Combinations of these agents

have been used for several years; however, the point of this paper is to stress the advantages of the light anesthesia which an appropriate combination can effect. This level of anesthesia requires minimal amounts of each agent so that toxic manifestations seldom occur.

The requirements of each component of surgical anesthesia vary with the individual. For example, more sedation is required for the very apprehensive patient than for the patient who is calm. A low threshold for pain is compensated for by additional basal narcosis and/or additional quantities of the analgesic agent. If the patient is carried in the plane of analgesia from which he can be readily aroused, the incidence of arrhythmias and other abnormal circulatory and respiratory reactions is minimal.[5] The ideal general anesthesia is one that yields amnesia and surgically adequate analgesia, and requires the least amount of anesthetic agent.

In "Brain Metabolism and Cerebral Disorders," Himwich[6] describes the slow progressive depression of the neuraxis which results from the physiologic breakdown induced by insulin hypoglycemia. This slow deterioration is equivalent to a four-hour induction of anesthesia. From Himwich's observations, combined with the principles defined by Davis,[7] it appears that general anesthesias inactivate the strata of the nervous system sequentially and in the reverse order of their phylogenetic origin. "The more primitive layers may remain functionally intact while the higher layers are more or less completely depressed. Nuclei contained in the brain usually are stimulated before they are depressed by ether. Pentothal caused no excitation of the lower levels and with finely graduated doses, its action on the cortex can be outlined."[7]

(1) Hypnosis. Thiopental sodium is given slowly with the effect of depressing the cerebral cortex and gradually separating the patient's consciousness from his environment. Since the stage of excitement (as seen in ether anesthesia) is absent, the corresponding peripheral autonomic signs do not appear. The physiologic processes slow down to basal levels. The increased pulse rate and the hyperpnea caused by apprehension subside, and the patient becomes calm. It is important to realize however that at this point the patient can be aroused and will respond coherently to questioning. At no time is the barbiturate amnesia carried to the point of unconsciousness. Pentothal is not used to lower the threshold for pain; its principal function is to erase the memory of the procedure and of the placement of the local anesthesia in the site of the incision.

(2) Analgesia. Nitrous oxide is given with oxygen to provide adequate analgesia for intra-abdominal procedures. Since local injection of procaine hydrochloride provides the necessary anesthesia of the skin, the inhalation of nitrous oxide is more than sufficient to cover the pain and discomfort of manipulation in the body cavities. When pentothal provides the necessary hypnosis, nitrous oxide is administered as a smaller percentage of the inhaled mixture than if it were used alone. At the beginning of a procedure, relatively large proportions of nitrous oxide (nitrous oxide 80 per cent, oxygen 20 per cent) are usually necessary, but at all times the oxygen is maintained at 20 per cent or

PREOPERATIVE MEDICATION:

M. S. ....1/8....gr.....12:30....p.m. Demerol.....mg.....m
A. S. ....1/200....gr...12.30..p.m. Other.....

PREOPERATIVE SURVEY: Good..... Fair....X.... Poor.....

	Yes	No	
Respiratory		X	Old Coronary
Cardiovascular	X		Infarction
C. N. S.		X	
G. I.	X		Cholelithiasis
Metabolic		X	Com. Duct Stone
G. U.		X	

ANESTHESIA COMPLICATIONS:

Yes....X.... No..... Change anesthesia....No.....
Remarks:— Period Hypotension (3-4 min.) to 80 mm. Corrected with Neo-syneph.

No. .....660-904.....Date .....Dec. 22, 1953.....
Name .....H. S.....
Surgeon .....Dr. Hoerr.....
Anesthetist .....Dr. Wasmuth.....
Operation .....Cholecystectomy & Cholangiogram.....

I. V. ANES 14cc....2....% Surital..... Pent. X.....
Nemb..... Seconal..... Other.....
Induced .....2:05 .....p.m. Completed .....4:10 ..... p m.
Total fluids .....1000.....cc. Total blood.....1/m.....cc.

Age ....68 years.... Color.....White..... Room.....406.....
Sex .....Male.....

SPINAL ANESTHESIA: Proc.....mg. Pont.....mg. L..... P..... .....G. N. Catheter cm.
Level..... Remarks:

ENDOTRACHEAL:
Yes .....X..... No..... Orotracheal .....X..... Nasotracheal..... Cocaine .....X..... Curare..... Other..... Pent. ....X..... Awake ....X.....

Methods		Spec. Procedure		Pentothal	X	Metycaine		Nembutal	
I. V.	X	Blood Venous		Nitrous Oxide	X	Intracaine		Seconal	
INH	X	Arterial		Ether		Xylocaine		Barbiturate	
Spinal		Cont. Hypo.		Curare	X	Cocaine	X	Nitrites	
C. Sp.		Cut Down		Vinethene		Efocaine		Aminophyllin	
Rectal		Plasma Expander		Trilene		Morphine		Alcohol I. V.	
Block	X	Respirator		Avertin		Demoral		Digitalis	
		EKG	X	Procaine	X	Atropine		Proc. Amide	
		EEG	X	Pontocaine		Scopolamine		Vasopressor	X
				Surital				Nalline	

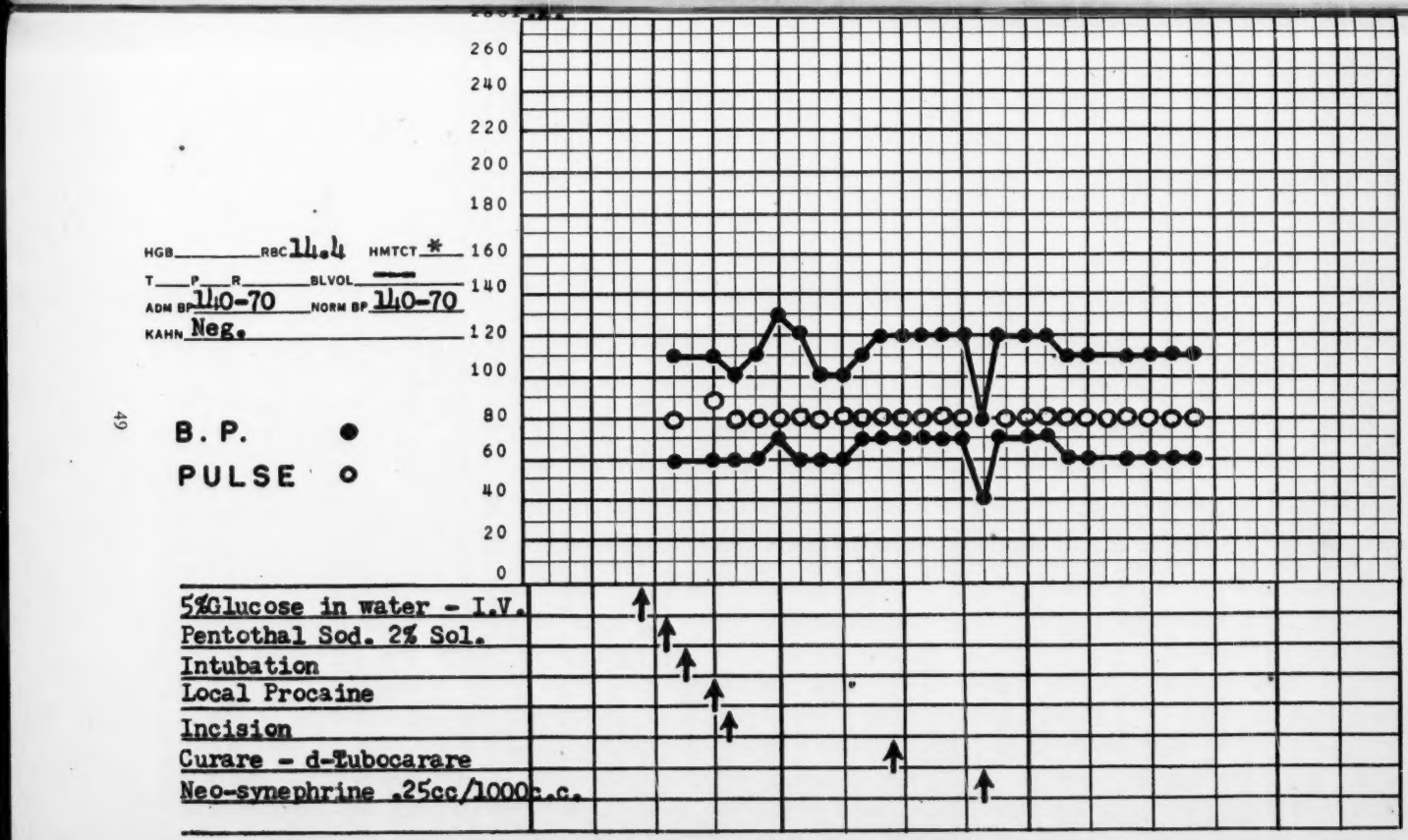

Fig. 1. Anesthesia record of the patient described in text.

above. Once the nitrous oxide has come into equilibrium with body nitrogen, the proportion can be reduced to 50 per cent: i.e., equal quantities of nitrous oxide and oxygen. This is an oxygen-rich mixture. Large flows are maintained in order to avoid the occurrence of respiratory acidosis, especially during open chest operations. Since nitrous oxide is not irritating to the pulmonary epithelium,[8] and the respiratory movements are not depressed, postoperative chest complications are not expected. The cough reflex returns soon enough after operation to prevent bronchial accumulations and postoperative atelectasis. Circulating blood and plasma volume are not affected by analgesic doses of nitrous oxide.[3] In addition to these advantages, nitrous oxide is noninflammable, inexpensive, and an excellent general analgesic. No other agent possesses all these fine qualities.

(3) **Relaxation.** Curare and curare-like substances may be given for relaxation if necessary. These muscle relaxants should be given cautiously and in small amounts. The circulatory effects of these agents should not be discounted, especially in the poor-risk surgical patient or during cardiac surgery.

TECHNIC

Premedication is morphine and atropine intramuscularly administered one hour before operation in doses adjusted to body weight. When the patient is brought to the operating room, an arm is cannulated for an intravenous drip and thiopental sodium is given through the tubing in repeated doses of 60 mg. (3 cc. of 2 per cent solution) until the patient becomes drowsy. The larynx is sprayed with cocaine (4 per cent) in an amount less than 5 cc., and the trachea is entered with a cuffed tube. The nitrous oxide-oxygen mixture is started and deep respiration is maintained by compression of the bag without re-breathing. The surgical field is prepared and procaine infiltration begun. The aim is to maintain a state in which the patient can still respond to questions by appropriately moving his head. To this end the proportion of nitrous oxide is slowly reduced and that of oxygen increased until a steady state ensues. Even at the time the surgeon is manually dilating the mitral valve or doing an esophagojejunal anastomosis through a wide thoraco-abdominal incision, the patient will nod correctly to confirm or deny suggestions made as to the color of a card held in his view. Meanwhile he is spared completely the knowledge and sensation that operation is being performed and, when questioned, will indicate that he is neither afraid nor anxious. The sensorium is so blocked that he is incapable of emotionally appreciating pain and the stage of anoci-association is reached. The physiologic aberrations of deep anesthesia do not occur.

CASE REPORT

A man, 68 years of age, was admitted to the Cleveland Clinic Hospital for removal of stones from the common duct. However, six months prior to this admission the patient had suffered a coronary occlusion. The electrocardiogram revealed signs of a posterior infarct.

Fig. 2. Electroencephalogram during anesthesia.

Because this patient was a poor surgical risk, light anesthesia utilizing the pentothal-nitrous oxide technic was suggested. The premedication was morphine 1/6 gr. and atrophine 1/100 gr. For purposes of record, electrodes were placed in his scalp, and a preinduction electroencephalogram was taken; thiopental was given in very small amounts until the patient was asleep. Intubation was performed. Nitrous oxide was started in the 80-20 mixture. Local infiltration of the anterior abdominal wall was carried out by the surgical team and a right rectus incision was made. The patient experienced no pain during the procedure, and the pulse rate and blood pressure only momentarily fluctuated more than a few points (fig. 1). Electroencephalograms were made at various sites during the course of operation; the tracings indicate that a constant plane of anesthesia was being maintained. At the end of the procedure, a small amount of thiopental sodium was given to document the level of anesthesia by eliciting the characteristic low-frequency but high-potential waves of pentothal "excitement." The patient was soon restored to consciousness but he was not aware that the operative procedure had been performed. The endotracheal tube was removed and the patient complained of slight abdominal pain. The postoperative course in the recovery room was without incident. The blood pressure of 100/70 was maintained. No postoperative complications were experienced.

DISCUSSION

The encephalographic interpretation of anesthetic levels, as originally described by Faulconer,[8] allows the anesthesiologist to document with relative accuracy the stages of anesthesia with the various agents. In the study of this type of anesthesia, the preceding case offers a typical example. Comparing this encephalogram (fig. 2) with those published by Kiersey,[9] we find that this patient was in the earliest levels of anesthesia, levels supposedly not adequate for surgery. However, with the combination of the precedingly described technic and agents, a type of anesthesia was produced which could be described as "amnalgesia" since it combines amnesia or hypnosis (predominantly produced by pentothal) and analgesia (produced by local procaine and the inhalation of nitrous oxide). While the patient can be roused by questioning, manipulations of the viscera do not disturb him. At least when asked whether he is experiencing pain, the answer is always in the negative. Perhaps the cortical depression of the combined anesthetic agents performs a medical prefrontal lobotomy and destroys the association of pain as something disagreeable or noxious. Nevertheless, a major operation was uneventfully performed at this level and the level itself established by change in the electroencephalogram which followed the injection of additional thiopental sodium at the end of operation. In the case described, the surgical procedure was carried out in Pattern I in the Kiersey-Faulconer classification.[9] Electroencephalographically, this stage is characterized by fast spiked waves of mixed frequency between 10 and 30 cycles per second and of amplitudes up to 75 to 80 microvolts. This pattern (fig. 2) establishes that the level of "amnalgesia" is well above surgical level of unassisted thiopental anesthesia.

The complications attributable to this type of anesthesia are minimal. Central nervous depression is largely cortical; since thalamic and hypothalamic

centers are not excited, this method of anesthesia is adaptable to most types of surgery. Our experience in using it for mitral commissurotomies has been excellent. There have been no cases of cardiac arrest or serious cardiac arrhythmia in the more than 90 valvulotomies.[5] Experiences in other types of surgery have been similarly good. It follows our general rule that all anesthesia is kept as light as is consistent with good anesthetic principles and with surgical demands.

SUMMARY

A method of light anesthesia is described which incorporates all of the surgical requirements of safe anesthesia. Amnesia or hypnosis is supplied by minimal amounts of thiopental sodium; analgesia is produced with nitrous oxide inhalation; relaxation, if needed, is derived from the use of curare and curare-like agents.

The abnormal physiologic variations of blood pressure, pulse rate and respiration which characterize deep levels of anesthesia are not evidenced. Although they can be aroused, these patients are not conscious of the surgical procedures being performed on them and are not suffering any pain.

The technic is exemplified by a case report and electroencephalographic evidence that a major operation can be done at a stage of light anesthesia which corresponds to Pattern I of the Kiersey-Faulconer chart.

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and

J. R. LEONARDS, Ph.D.*

THIS article is concerned only with the removal of edema that either has been resistant to the usual forms of treatment, or is of such a nature that the latter are contraindicated for the patient. When salt-free diet, sodium-binding resins, digitalis, or mercury preparations fail, or cannot be used, artificial kidneys or other dialyzing methods may be useful; they have the additional advantage that during dehydration, retention products are also removed. (For details of technics see references 1 and 2.)

Dialysis With Hypertonic Solutions to Remove Edema

Most artificial kidneys use dialysis, which means purification through a semipermeable membrane, with the patient's blood on one side of a cellophane membrane and rinsing fluid on the other side.[1-4] In peritoneal lavage, dialysis occurs through the peritoneum and walls of the numerous capillaries in the subserosa. Electrolytes will equilibrate on both sides of the membrane; urea and other retention products are removed from the blood by the dialysis. Five to eight hours of treatment will suffice to reduce the patient's blood urea from very high levels to nearly normal values with efficient artificial kidneys.

In the artificial kidneys that use dialysis only, there is no difference in hydrostatic pressure between the patient's blood in the cellophane tubing and the rinsing fluid. Under these circumstances, while urea is moving across the cellophane from the blood to the rinsing fluid (fig. 1), water is being attracted to the uremic blood, as it will always pass from a place of lower concentration of solutes to one of higher concentration. The higher osmotic pressure on the side of the blood can be overcome by adding glucose to the rinsing fluid: an excess of glucose will reverse the process and water will be attracted from the blood into the rinsing fluid.

So far, we have discussed the cellophane as though it were a semipermeable membrane; however, it is impermeable only for larger molecules such as proteins. In fact, both urea and glucose move through the membrane quite rapidly. Figure 1, helpful as it is, does not give a true picture of the situation in the artificial kidney; but even when the membrane is not purely semipermeable,

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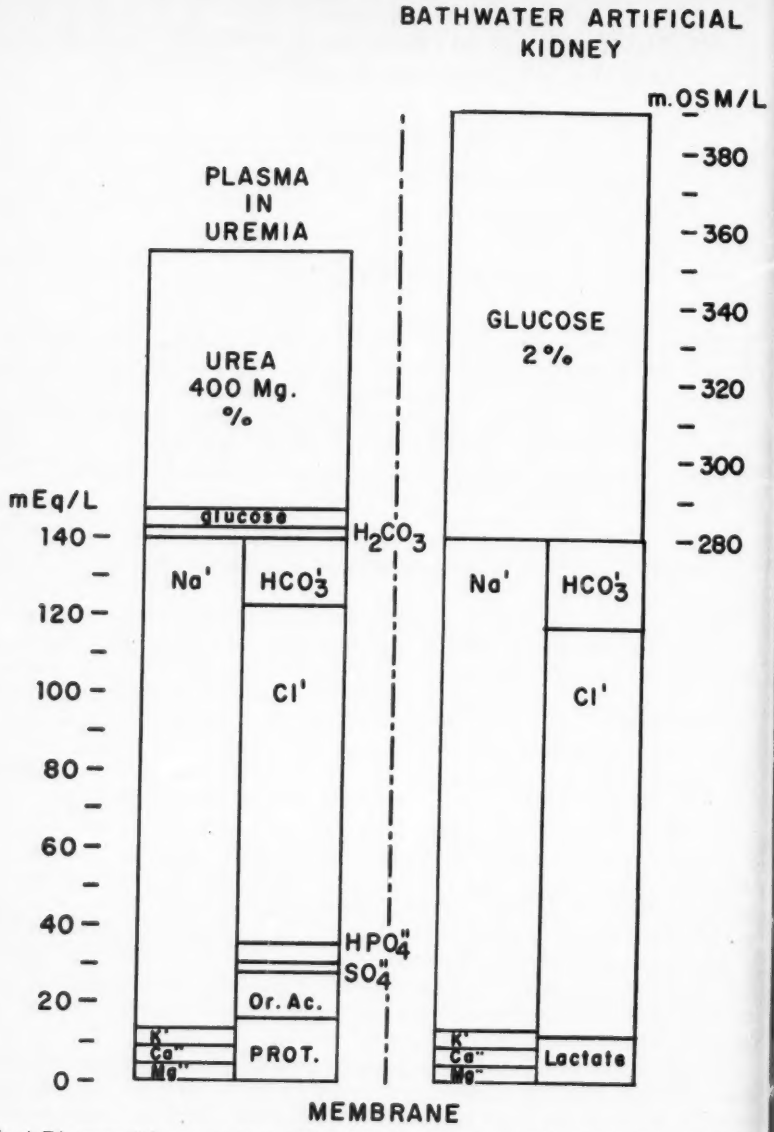

Fig. 1. Diagram of the composition of blood plasma of a patient with uremia, left, and of the rinsing fluid of an artificial kidney or peritoneal lavage, right. It will be noted that the Na is low, as it is in most patients with uremia. Urea moves to the right, and glucose to the left, and the osmotic difference causes a fluid shift from left to right.

it is still possible to effect a movement of water from the blood plasma to the rinsing fluid by adding glucose to the latter. This principle was demonstrated by Van den Bossche and one of us[5] in 1946, by means of the small dialyzing apparatus in which the volume of blood plasma that circulated along a cellophane membrane could be accurately measured. The rinsing fluid also circulated continuously and any desired small difference in hydrostatic pressure between the blood plasma and the rinsing fluid could be accurately set and maintained. When identical solutions were run on both sides of the membrane in this apparatus, no changes in volume occurred. However, when blood plasma was used in one compartment and glucose was added (4 per cent) to the usual composition of the rinsing fluid, a continuous fall in the plasma volume took place (fig. 2). The experiments established that it is possible to remove water from the blood plasma by adding extra glucose to the rinsing fluid of a dialyzing system even when the membrane used is permeable for glucose.

Rotating Type of Artificial Kidney Using Hypertonic Rinsing Fluid. The rotating type of artificial kidney depends on dialysis only for the exchange of electrolytes and the removal of retention products. There is no hydrostatic pressure difference on the two sides of the cellophane. It has often been reported[1,2,6,7] that pulmonary edema was reduced by treatment with the artificial kidney, especially when extra glucose was added to the rinsing fluid. Lewis and collaborators[8] described a loss of weight of 4 Kg. in 6 hours. To remove such large quantities of fluid, up to 5 per cent glucose in the rinsing fluid was necessary. As a consequence, the glucose concentration of the blood coming out of the artificial kidney is greatly increased; the patient's blood sugar may increase to more than 700 mg. per cent. Merrill and associates[6] gained the impression that high concentrations of glucose caused vomiting and drowsiness in the patient. This concurs with our experience. We now combat the high blood sugar levels with insulin intravenously, 10 to 20 U. every half hour; the blood sugars should be determined.

The rotating type of artificial kidney may conveniently be used to remove up to two liters of edema fluid per dialysis by adding 2 or 3 per cent glucose to the rinsing fluid. The following case history offers an example.

Case 1. A 31 year old woman accidentally drank carbon tetrachloride after sensitizing herself to it by the use of excessive doses of alcohol. She became anuric and vomited persistently. On the 11th day after the onset of anuria, she was icteric, irrational, and extremely difficult to manage. The abdomen was distended; blood pressure was 160/80 mm. Hg, and the urine volume had slowly progressed from 2 to 180 ml./24 hours. There were extensive subcutaneous ecchymoses. On the 12th day she was treated with the rotating type of artificial kidney, 2 per cent glucose being added to the rinsing fluid. Blood urea was reduced from 270 to 150 and creatinine from 26 to 16 mg./100 ml.; serum sodium was purposely maintained at the low level of 126 mEq./L., and CO_2 combining power increased from 13.5 to 16 mEq./L. as a result of the 5-hour dialysis. The patient lost 6 pounds (2.7 Kg.) in weight. Her clinical condition the day after treatment was greatly improved. Diuresis started a few days later and recovery was uneventful.

While in this case the primary indication for treatment with the artificial kidney was the necessity to remove retention products, the additional removal of 6 pounds of edema fluid was certainly most helpful.

Peritoneal Lavage Using Hypertonic Rinsing Fluid. It is possible to remove edema fluid with peritoneal lavage using the same principle of adding glucose to the dialyzing fluid. In the laboratory, using the intermittent peritoneal lavage as described by Grollman, Turner, and McLean,[9] it is possible to maintain a nephrectomized dog in a controlled state of hydration by varying the amount of glucose that is added to the usual electrolyte composition of the rinsing fluid. Thus, if glucose is added (2 to 5 per cent) to the rinsing fluid, it is almost certain that two hours later a larger volume of fluid may be removed from the peritoneal cavity than that which was instilled. Peritoneal lavage is effective, though not as practical in patients as in dogs. The patient's discomfort often required use of a continuous rather than an intermittent method.[1,2,10]

Case 2. A 16 year old boy was admitted to Cleveland Clinic in the terminal stage of a subacute glomerulonephritis with uremia and nephrotic syndrome. Many methods, including the administration of cortisone, had been unsuccessfully used to reduce the edema that had become so severe that respiration was difficult.

To remove ascites a plastic cannula was introduced into the abdomen and 1100 and 850 ml. of fluid, respectively, were drained on consecutive days. An x-ray of the chest showed pulmonary edema and marked cardiac enlargement. Respiration became exceedingly difficult, and as a tube was already in the abdomen, it was decided to treat the patient with peritoneal lavage. The composition of the rinsing fluid in mEq./L. was as follows: sodium 124; potassium 1.3; calcium 4.5; magnesium 2.7; chloride 104; HCO_3 20; HPO_4 1.8; and lactate 6.7. In the beginning of the treatment, 5 per cent glucose was added to the rinsing fluid—later 7.5 per cent. This greater amount caused pain and the 5 or 6 per cent glucose was again used. Total measured in- and outflow over the two-day period was 20 liters. However, large unmeasured amounts leaked out and were lost into the bed. The patient's weight decreased from 164 to 149 pounds. About 64 Gm. of urea was removed. The urea concentration of the abdominal fluid, which is a rough measure of the blood urea, decreased from 360 to 260 mg. per cent. The following day the pain in the abdomen gradually subsided, and the patient was in much better clinical condition than before, although there was still much edema in the lower extremities. He ate well and even asked for more food. His weight continued to fall the following days, but the urine output decreased. On the fourth day after peritoneal lavage, his condition began to deteriorate rapidly and he died on the fifth day.

The postmortem examination revealed that the patient had uremic pericarditis, hydrothorax, pulmonary edema, and early bronchopneumonia. Fifteen hundred ml. of fluid was found in the peritoneal cavity, but there was no peritonitis. The underlying disease was subacute glomerulonephritis.

It may be remarked that while in this case the edema was the primary indication for treatment with peritoneal lavage, uremia was also relieved to some extent.

Case 3. A woman of 35 years of age cleaned a rug with carbon tetrachloride on a warm day, and then drank a few glasses of beer. On the 13th day after inhaling the carbon tetrachloride fumes she was sent to the Cleveland Clinic. On arrival she was extremely

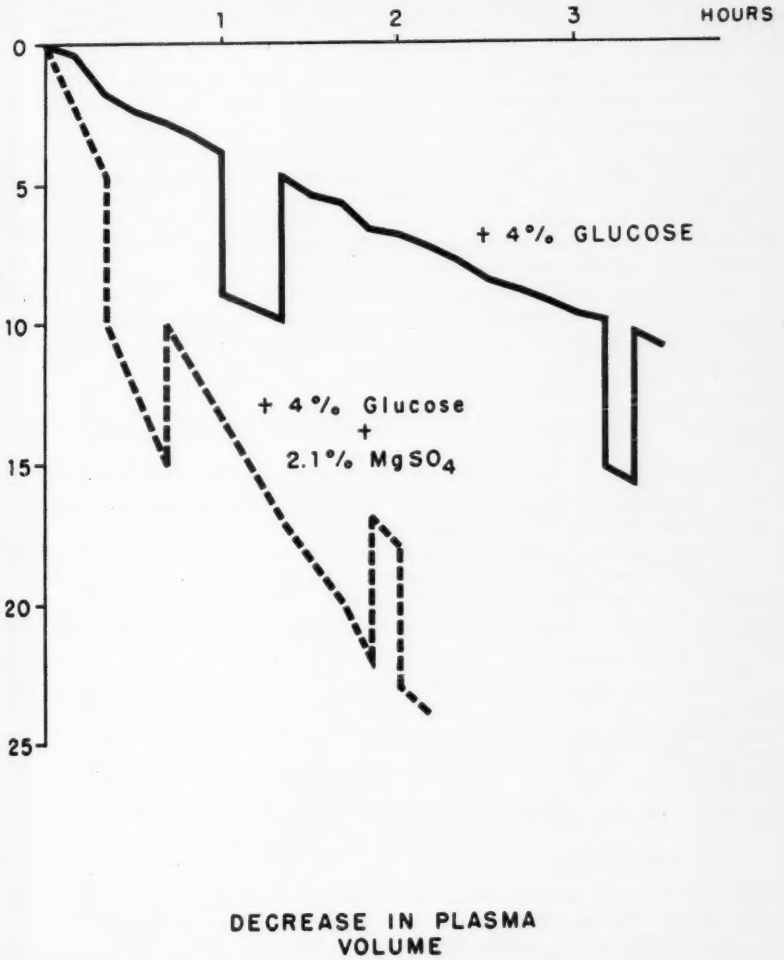

Fig. 2. One of the graphs published in reference 5. The volume changes in ml. are indicated of 200 ml. of blood plasma circulating along a cellophane membrane (254 sq. cm.) while "rinsing fluid" circulated on the outside of the membrane and the colloid osmotic pressure of the blood plasma was, in this particular experiment, compensated for with a hydrostatic pressure difference. Under these conditions the volume of the blood plasma remained constant during circulation. However, when 4% glucose or 4% glucose plus 2.1% $MgSO_4$ was added to the rinsing fluid, a decrease of the plasma volume took place. The sudden decreases and increases in volume indicate checks on the accuracy of the apparatus when 5 ml. of plasma was withdrawn or added.

cyanotic, severely dyspneic and had rales in both lungs. There was edema and the abdomen was distended. Urine output had been negligible. The blood pressure was 130/70 mm. Hg, but sometimes it dropped to under 100. Peritoneal lavage was begun immediately while the patient was in an oxygen tent. The electrolyte composition of the rinsing fluid was the same as that used in the patient mentioned previously (case 2). Glucose was used in the concentration of 5.1 per cent. The inflow of the peritoneal fluid was 8.1 L.; the outflow was 11.95. There was 3850 ml. of fluid removed during approximately 10 hours of peritoneal lavage. Serum sodium increased from 111 to 123 mEq./L.; potassium decreased from 6.8 to 6.3. The blood pressure the next morning was 150/80 mm. Hg. It seemed that the immediate danger caused by pulmonary edema was subsiding. Treatment in the oxygen tent and with antibiotics was continued. Fluid intake was restricted. Urine output gradually increased and she made a complete recovery.

It is our impression that the removal of 3850 ml. of fluid by peritoneal lavage marked the turning point in recovery from the pulmonary edema and extreme dyspnea, and made the patient's condition amenable to further treatment.

Ultrafiltration With Artificial Kidney to Remove Edema

We speak of filtration instead of dialysis when a pressure difference exists on the two sides of a membrane and fluid moves from one side to the other. It will be recalled that in the glomerulus, ultrafiltration takes place; this process is imitated in some kinds of artificial kidneys. Malinow and Korson[11] constructed an artificial kidney that worked with filtration *only*. It would be quite useful in the removal of edema; however, it is of little use in the treatment of uremia since the filtering process is so much slower than is dialysis in the removing of retention products.

Many types of artificial kidneys have some pressure difference across the cellophane membrane. Their effectiveness in terms of volume of ultrafiltrate removed depends upon the filtering area and upon the pressure difference. Not all types will stand the rather large pressure difference required to make them effective. Alwall (Sweden) brings about ultrafiltration by producing suction on the rinsing fluid side of the membrane.[12] He accomplishes this by lowering the outflow tube for the rinsing fluid to the next lower floor of the hospital, thus creating a siphon.

In the artificial kidney described by Skeggs, Leonards, and Heisler[3] it is possible to apply negative pressure from a water aspirator to the outflow tank of the rinsing fluid while partially clamping the inflow. It also would be possible to constrict the outflow line returning blood from the artificial kidney to the patient, and pump the blood in at a higher pressure, although this is less efficient. The cellophane membranes are, of course, supported by fine ridges; otherwise the space that contains the blood would expand. By this means it is possible to remove 1000 to 1200 ml. of ultrafiltrate from the blood per hour while the blood is being dialyzed at the same time. One has to be extremely careful not to dehydrate the patient too rapidly. In the laboratory, normal dogs could be killed by removing about 800 ml. of ultrafiltrate from the blood stream. Dogs rendered edematous by decreasing their plasma proteins would

stand removal of a larger volume;[13] they died, however, after removal of 2000 ml. of ultrafiltrate even when approximately 5000 ml. of edema fluid was present.

In treating patients with this equipment the hematocrit should be determined repeatedly to avoid too rapid dehydration and too great a reduction of circulating blood volume. Guided by the hematocrit and the blood pressure, we found it useful to replace some of the reduced blood volume with dextran. Thus far, four patients with edema have been treated with the help of ultrafiltration.

Case 4. A 45 year old woman had been under treatment since 1918 for recurrent congestive heart failure on the basis of rheumatic heart disease. She was readmitted to the Cleveland Clinic on October 18, 1952, with severe cardiac decompensation, and was treated with digitalis, salt restriction, and mercury preparations. After some initial improvement, however, her weight steadily increased from 122 to 134 pounds, and the blood urea rose to 120 mg./100 ml. She was very short of breath and developed massive edema of the legs which were tense and painful. All attempts to reduce the edema failed. On November 26, 1952, before treatment with ultrafiltration, the pulse was weak, the blood pressure could not be obtained (later it was 100/80 mm. Hg) and she was severely cyanotic. There were rales over the chest and very extensive edema over the lower part of the body. The liver was large; ascites was present.

In five hours of combined ultrafiltration and dialysis, 4 liters of ultrafiltrate was removed. The blood pressure continued to be low, 82/48 at the end of treatment. The patient was tired but otherwise all right. She sat in a chair immediately after treatment. During the ultrafiltration, after the initial hematocrit reading of 41 had increased to 46 per cent in one hour, an infusion of dextran was given. The rate of ultrafiltration was decreased and the hematocrit was maintained at 46 for the remaining period of the treatment. The patient's weight decreased from 134 to 128 pounds. Urine output, which had been 350 ml. the day before, was 500 ml. on the day of dialysis and ultrafiltration. On subsequent days it was only 50, 37, 50, 125, and 130 ml., respectively. Her weight stayed down for several days and she felt better. The edema in the legs was decreased and she had no pain. Urine output slowly increased to 900 ml., but her general condition regressed to that before treatment with the artificial kidney. The dialysis reduced the blood urea from 120 to 42 mg. per 100 ml.

In this case there was a definite but temporary improvement of the clinical condition of the patient, lasting about three or four days immediately after treatment with ultrafiltration and dialysis. However, postdialytic oliguria counteracted the improving effect of treatment.

Case 5. A 45 year old man who had been a professional boxer in his younger years began to show the signs of chronic nephritis, hypertension, uremia, and anemia four months prior to admission to the Cleveland Clinic, February 24, 1953. He then had congestive heart disease, gallop rhythm, edema, and continuous vomiting. He could retain nothing fed by mouth, and he was maintained with invert sugar (Travert*) 20 per cent for 10 to 14 days. He developed a cerebral accident causing partial paralysis of the legs and retention of urine. His condition progressively deteriorated. On March 20, 1953, he was treated with the rotating type of artificial kidney. After treatment he was able to eat and did not vomit. The mobility of his legs gradually improved. He had

* *We are indebted to Dr. Robert P. Herwick, Baxter Laboratories, Inc., Morton Grove, Ill., for providing the 20 per cent Travert.*

a noticeable postdialytic oliguria and, as his fluid intake was not sufficiently restricted after treatment, he became more markedly edematous. Therapy with sodium lactate as described by Neubauer[14] was attempted; edema increased and the blood urea went up to the level where it had been before treatment with the artificial kidney; he developed pulmonary edema, pericarditis and Cheyne-Stokes respiration.

On April 2, 1953, he was treated with the stationary type of artificial kidney (dialysis and filtration) with the dual purpose of removing retention products and edema; 8100 ml. of ultrafiltrate was removed in 8½ hours. Hematocrit reading increased from 21 to 26 per cent and was maintained at 24 with the help of 100 cc. dextran intravenously. There were no undesirable reactions but a rise in temperature of 1 degree F. The night after treatment he was somewhat more confused mentally than he had been before treatment. There was great improvement of the respiratory rate, but, because of his mental confusion, it was decided not to give him a second ultrafiltration as had been originally planned. There was a slight reduction in the urine production the days after dialysis and ultrafiltration but certainly not a very evident postdialytic oliguria. His fluid intake was now restricted and edema did not increase. His blood urea went up again in the course of a week; however, he was not as uncomfortable as he had been prior to treatment. In regard to blood chemistry during treatment with the artificial kidney, the blood urea was reduced from 345 to 225 mg./100 ml., and the creatinine from 20.5 to 14.7 mg./100 ml.

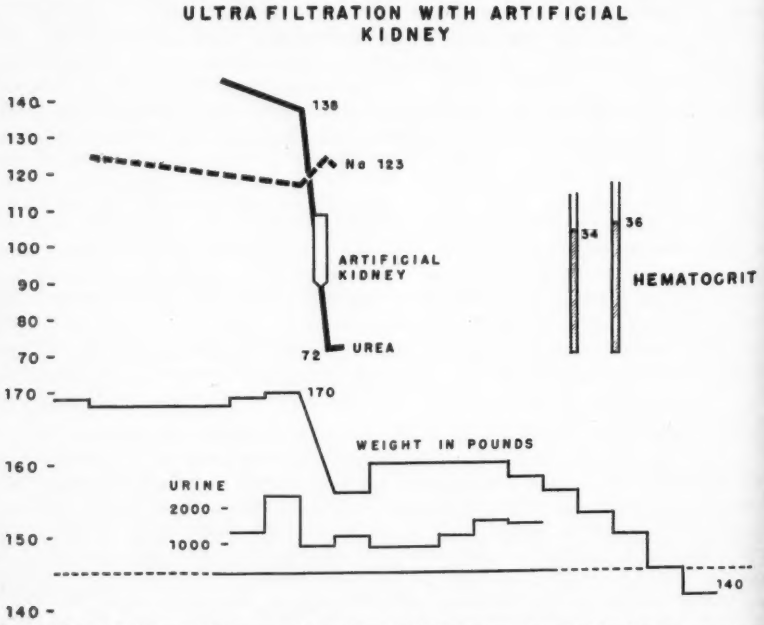

Fig. 3. (Case 6) 47 year old man with polycystic kidneys and intractable edema was given one treatment with the dialyzing-filtering type of artificial kidney. Fall in weight during treatment is indicated; it marked the beginning of a fortunate but unexplained progressive elimination of the edema. Urea is indicated in mg. per hundred ml. Na is indicated in mEq. per liter.

In retrospect, it may be concluded that the treatment with the rotating type of artificial kidney caused the disappearance of the vomiting, which had been the most important clinical symptom before treatment. The stationary artificial kidney was mainly used to relieve the edema that had caused serious respiratory embarrassment. This was accomplished and the edema did not recur during the further downhill course of the disease.

Case 6. A 47 year old man was known to have polycystic kidneys for at least 10 years. He had been maintained on a high-caloric, low-protein diet for a year and a half. He entered the Cleveland Clinic, September 25, 1952, with extensive edema, mostly in the lower part of the body. With digitalis, bed rest, low-sodium diet, and Mercuhydrin, his weight was reduced from 172 to 168 pounds. After that, it was impossible to reduce it further. Blood urea varied from 186 to 222 mg. per 100 ml. There was ascites with drum-like tension of the abdomen. He was treated with the stationary artificial kidney with simultaneous ultrafiltration and dialysis for 7 hours (fig. 3). The usual composition of the rinsing fluid was used with 135 mEq. of sodium per liter. During the day he was treated, he lost 13½ pounds in weight. The amount of ultrafiltrate removed could be measured during the second half of the procedure and amounted to almost 1200 ml. per hour.

Toward the end of the treatment, the patient enjoyed eating a ham sandwich allowed for the occasion. During four days following treatment with the artificial kidney, there was some increase in weight, but later there was a steady decrease. He left the hospital much improved without edema, and able to take a 1000 to 2000 calorie diet, and with a blood urea content of 90 mg. per 100 ml. A dermatitis developed which caused his death six weeks later.

In this case, it seems as though some vicious circle was broken; we have no explanation as to why there was a sudden increased ratio of urine volume to fluid intake. The edema did not recur.

Case 7. A 48 year old man came to the hospital on August 27, 1953, with the diagnosis of chronic glomerulonephritis with nephrotic syndrome. He was uremic and edematous; he vomited and had felt miserable for several weeks. A high-caloric, 20-gram protein diet was first prescribed. But, on account of anorexia and vomiting we did not succeed in feeding him more than 500 or 1000 calories per day. A course of watermelon was tried; there was increase in diuresis but no decrease in weight. It was thought that his clinical condition might be improved greatly if the edema was reduced. Attempts to remove edema began with paracentesis. Two and one half liters of fluid was removed and the patient's weight was reduced from 190 to 182 pounds. Next, treatment with the filtering type of artificial kidney was given (fig. 4). Eight hundred to 1000 ml. of ultrafiltrate per hour was removed during five hours of filtration and dialysis; body weight was further reduced from 182 to 169 pounds. To avoid postdialytic oliguria, urea was added to the rinsing fluid in a concentration of 120 mg./100 ml.[15] The patient's serum electrolytes were practically unchanged by the procedure.

The following days, there was a marked change in the patient's general well-being. His appetite increased and he took with pleasure 1500 and, later, over 2000 calories per day. Diuresis was a little more than before the watermelon period. There was no postfiltration oliguria, perhaps thanks to the addition of urea to the rinsing fluid as indicated above. His weight remained stable for five days and then increased on the sixth. The following day, the first of two courses with ACTH was started. After the second, diuresis occurred. Unfortunately, it did not last long. However, after his return home he lost considerable edema; he followed a 2000-calorie, 40-gram protein diet. He was able

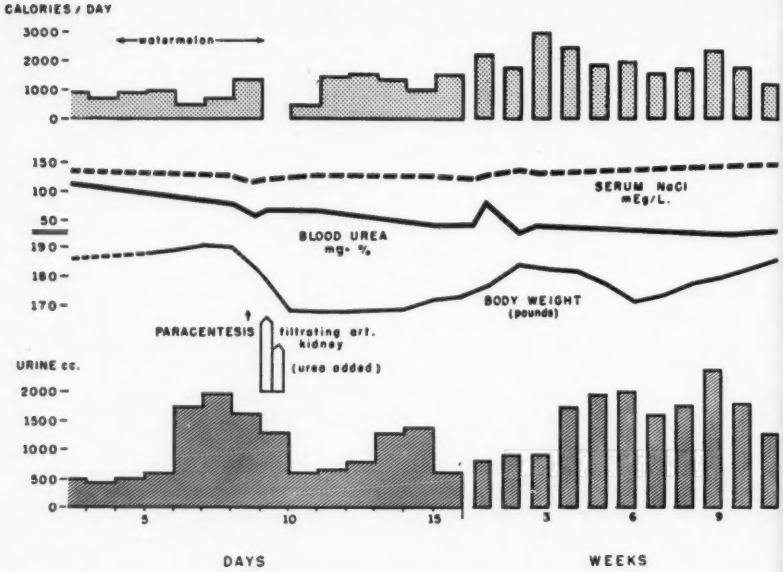

Fig. 4. (Case 7) 48 year old man with chronic glomerulonephritis and nephrotic syndrome; greatly incapacitated by edema. The caloric intake as indicated before treatment is too optimistic as vomitus was not taken into account. Note the increased diuresis during the watermelon diet, without concomitant fall in weight. After one treatment with dialysis and filtration his clinical condition improved markedly. Note that his blood urea did not fall during dialysis and filtration because of the addition of urea to the rinsing fluid. There was no postfiltration oliguria.

to do some of his work until almost two months later when the edema began to recur. He is now under treatment for this recurrence.

In this case, the improvement in the patient's well-being, which was perhaps partly due to the removal of some retention products but mostly due to the removal of the edema, made his condition amenable to further treatment. Despite recurrence of the edema two months later, his general condition was very much better than it was prior to treatment with filtration and dialysis.

SUMMARY

Edema, otherwise intractable, may be treated by:

1. A dialyzing type of artificial kidney with glucose (2 to 5 per cent) added to the usual composition of the rinsing fluid. Losses of weight of 4 to 5 Kg. have been reported in the literature and an example is given in which a loss in weight of 2.7 Kg. was effected in one treatment.

2. Peritoneal lavage with glucose (2 to 10 per cent) added to the usual composition of the rinsing fluid. An example is given in which 4 L. was removed in 10 hours.

3. A filtering (and dialyzing) type of artificial kidney that will remove 1000 ml. of ultrafiltrate per hour. This is the most rapid method of dehydration. Hematocrit determinations are necessary to avoid undue hemoconcentration, reduction of circulating blood volume, and shock. Four patients were treated; all were benefited temporarily. In one patient, there followed spontaneous elimination of the remaining edema, and in another, continued improvement. Addition of urea to the rinsing fluid in one case may have helped to avoid postdialytic oliguria. Fluid restriction the first few days after the treatment is recommended.

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CLINICAL MANIFESTATIONS OF IDIOPATHIC HYPOPARATHYROIDISM

Report of a Case

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IDIOPATHIC hypoparathyroidism is an infrequently diagnosed disease with a high morbidity and a low mortality. Although secondary hypoparathyroidism became a prominent clinical entity with the advent of thyroid surgery, the primary spontaneous type continues to be uncommon. The scarcity of reported cases of idiopathic hypoparathyroidism was brought into focus by Steinberg and Waldron[1] in 1952 when in their complete review of the literature they were able to find only 51 cases to which they added one case of their own. They adhered to the following criteria for the diagnosis of the disease: (1) low serum calcium level; (2) high serum inorganic phosphorus level (greater than 5.0 mg. per cent for adults and 7.0 mg. per cent for patients under 16 years of age); (3) absence of renal insufficiency; (4) normal bones on roentgenograms (in order to exclude infantile rickets or adult osteomalacia); and (5) chronic tetany. The following case presents many of the classic signs and symptoms of the disease.

CASE REPORT

A 58 year old, white, married woman was first admitted to the hospital on June 10, 1952, because of recurrent convulsive seizures during the preceding 27 years. The seizures were thoroughly characteristic of grand mal attacks except for an occasionally associated period of confusion and disorientation lasting for hours or for days which at times required emergency hospital care. The convulsions occurred three or four times yearly, and in between the more severe episodes she experienced frequent tightness and spasm of the muscles of the extremities. These painful spasms lasted for hours or for days and often confined her to bed or chair. Subsequently, the joints became very stiff, leading to marked limitation of motion, particularly of the hip joints. She had been aware of occasional wheezing in the throat, probably due to laryngeal spasm.

The patient also had noted failing vision for at least 15 years, and almost complete blindness had developed during the preceding four to five years, requiring extraction of a cataract from the right eye in January 1952.

Her dental condition had deteriorated in early adulthood, and she was edentulous at 30 years of age. Other complaints consisted of intermittent dysuria, hematuria, and pain in the right flank during the preceding five years.

The family history disclosed that childhood convulsions had occurred in four of the patient's ten children. In two of the four children available for study, normal blood calcium determinations were found.

Physical examination revealed a well-developed, obese woman, who appeared chronically ill and older than her stated age. The temperature and pulse rate were

normal. The blood pressure was 154/86. The skin was dry and the hair coarse. There were generalized muscular rigidity and spasm, great limitation of motion in the hips, and crepitation of the large joints. The joints of the right hand appeared ankylosed in a position of carpopedal spasm, a condition which had been present and stationary for approximately six years. Chvostek's and Trousseau's signs were positive. Opthalmoscopic examination revealed an aphakic right eye. There was an almost mature cortical cataract of the left eye. Funduscopic examination revealed bilateral early papilledema. The remainder of the examination was essentially normal.

The serum calcium content was 4.9 mg. per 100 cc. and the serum phosphorus 6.8 mg. per 100 cc. An alkaline phosphatase determination was 5.6 Bodansky units. Pretreatment blood urea measurements were repeatedly within normal limits, and the urea clearance was normal. The urinalysis showed a heavy pyuria, and cultures of a catheterized urine specimen yielded a growth of *Esch. coli*. The hemogram was normal as were the serum proteins, serology, and plasma cholesterol.

A roentgenogram of the chest was essentially normal. An intravenous urogram revealed blunting of the calyces of the right kidney with retention of dye, suggestive of chronic inflammatory change. X-rays of the skeletal system showed degenerative changes in the lumbar spine, hips, and right knee. There was no demineralization of the bones. Roentgenograms of the skull were normal, and no intracranial calcifications were visualized.

The initial electrocardiogram was reported as showing a prolonged Q-T interval consistent with hypocalcemia.

The effect of the intravenous administration of 200 units of parathyroid hormone on the serum calcium and phosphorus is shown in figure 1.

Response to Parathyroid Hormone

	Fasting	After 200 U. Parathyroid Hormone I.V.			
		1 hr.	2 hr.	3 hr.	4 hr.
Calcium mg.%	8.2	8.6	8.6	8.9	9.2
Phosphorus mg.%	6.1	4.9	4.7	4.5	4.3

Fig. 1. The characteristic response of the serum calcium and phosphorus levels after the injection of parathyroid hormone in idiopathic hypoparathyroidism.

An electroencephalogram was reported as being borderline normal with no definite evidence of epilepsy or focal cortical lesion.

Initial treatment consisted of 6 drams of equal parts of calcium lactate and calcium carbonate daily with vitamin D, 150,000 units in divided doses. As illustrated in figure 2, the combination even with increased doses of vitamin D did not raise the serum calcium to satisfactory levels.

Dihydrotachysterol promptly brought the serum calcium within normal range and

the electrocardiogram reverted to normal. The patient was given a high calcium—low phosphorus diet from the onset of therapy.

The urinary tract infection was successfully treated with antibiotics. Extensive physical therapy to the joints resulted in considerable improvement. At the time of her discharge on July 23, 1952, the patient was instructed to do her own daily Sulkowitch test in order to reduce the likelihood of overtreatment.

She returned to the Clinic on September 17, 1952, and reported marked subjective improvement. There had been no convulsions or other symptoms of tetany. The serum calcium was 10.2 mg. per 100 cc. and the Sulkowitch chart revealed the reactions had remained 2 plus on most occasions. She was much more alert mentally, was walking with the aid of a cane, and was beginning to do some of her own housework. A cataract was extracted from the left eye on September 22, 1952, and the patient had an uneventful recovery. When last seen on February 10, 1953, eight months after the initial visit, rehabilitation of the joints was progressing rapidly. Funduscopic examination revealed normal optic discs, and the serum calcium was within normal range. The therapy program remained unchanged. A communication from the patient on December 22, 1953, stated that she was feeling very well and was continuing her treatment schedule.

DISCUSSION

The etiology of idiopathic hypoparathyroidism is unknown. No hereditary factor has been established although three reported cases occurred in siblings.[2] Theories concerning the relationship of birth trauma and infection have been advanced. There appears to be no significant difference in the incidence between the sexes, but the onset of symptoms appears to be somewhat earlier in women. Symptoms usually appear in the first or second decade, the average age being approximately 17 years. The average time between the onset of symptoms and the time of diagnosis is about eight years. In some instances the diagnosis is delayed for considerably longer periods. One patient[1] had complained of symptoms for 31 years, and our patient had had symptoms for 27 years prior to the recognition of the underlying disorder.

The most commonly noted clinical manifestation of idiopathic hypoparathyroidism is chronic tetany. It is a prominent symptom in 78 per cent of the cases reported in the literature. Generalized convulsions are reported in 52 per cent of the cases and many are misdiagnosed as idiopathic epilepsy. Laryngeal spasm and bronchial spasm are commonly associated tetanic equivalents. The Chvostek's and Trousseau's signs are positive. In some patients, grand mal convulsions are accompanied by increased spinal fluid pressure and papilledema, and these findings may suggest the presence of a brain tumor.[3,4] Papilledema is found in about 14 per cent of patients with idiopathic hypoparathyroidism and has been occasionally observed in surgical hypoparathyroidism. The papilledema usually regresses following therapy.

Although some authors, including Gotta and Odoriz,[5] report that there are characteristic electroencephalographic changes in this disorder, it is not generally accepted that these changes are diagnostic of hypocalcemia. Following therapy, the electroencephalogram may or may not return to normal.

In idiopathic hypoparathyroidism, as in uncontrolled postoperative hypo-

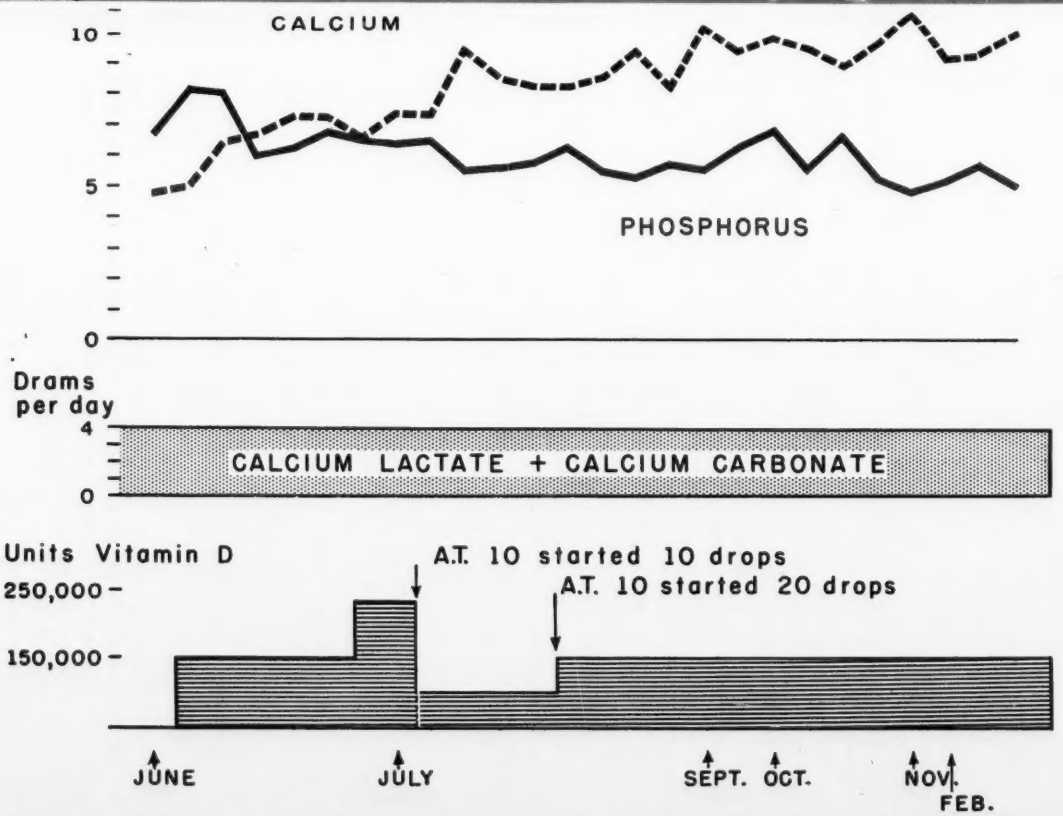

Fig. 2. Treatment chart of a patient with idiopathic hypoparathyroidism showing the serum calcium and phosphorus levels in relationship to therapeutic agents.

parathyroidism, cataracts are a common complication, occurring in about 50 per cent of the cases. Cataracts may develop even in extremely young patients having this disorder. Early diagnosis and adequate treatment to maintain the serum calcium in normal range are essential to prevent this complication.

Defects in dentition are a common accompaniment and have been recorded in one third of the cases. Other ectodermal dysplasias have been reviewed by Dietrich, Rice and Luton.[6] The nails are frequently brittle, deformed, and show horizontal grooving. Adequate therapy causes prompt disappearance of these defects. The skin is often dry and rough, closely resembling that of a patient with myxedema. The hair is observed to be sparse and dry in 25 per cent of the reported cases.

Roentgenograms of the skeletal system are usually normal. Occasionally there may be some generalized increased density of bone. At times cerebral calcifications are present, most commonly in the region of the basal ganglia. These changes are believed to be due to the deposition of a basophilic homogeneous material in and about the media and adventitia of the smaller cerebral arteries, with subsequent calcification of the deposits.[7] Subcutaneous calcification is rarely observed.

The electrocardiogram shows the typical findings of hypocalcemia with prolongation of the Q-T interval and normally shaped T wave.

Of the laboratory findings, hypocalcemia and hyperphosphatemia are the constant and diagnostic features. The average of the lowest serum calcium levels reported in previous cases is 5.6 mg. per 100 cc. and the highest serum phosphorus levels averaged 8.2 mg. per 100 cc. prior to treatment. The alkaline phosphatase determination is consistently normal.

There have been few opportunities for postmortem studies of this disease. Two cases showed complete absence of parathyroid tissue,[4,8] and a third, on microscopic study,[9] showed the parathyroid glands to be completely replaced by fat. This meager material supports the thesis that idiopathic hypoparathyroidism represents primary parathyroid failure. In contrast, a condition designated as pseudo-hypoparathyroidism, first described by Albright and his associates[10] in 1942, represents not a deficiency in parathyroid hormone but rather a lack of response of the kidney to adequate concentrations of the hormone, i.e. end-organ failure. The administration of parathyroid hormone to patients with parathyroid deficiency causes phosphate diuresis and a fall in serum phosphorus with a rise in serum calcium which is in accordance with the concept of the primary site of action of this hormone. In pseudo-hypoparathyroidism, these changes do not occur, suggesting that there is an adequate amount of circulating parathyroid hormone and that the primary defect is a failure of end-organ response. This observation forms the basis for the use of the Ellsworth-Howard test[11] in differentiating these two conditions. Biopsies of the parathyroid glands of two patients with pseudo-hypoparathyroidism also support the basic physiologic difference in the etiologies of the two conditions.[12] In one case, glandular tissue appeared to be normal, and in the other it appeared to be hyperplastic. Reynolds and his associates[13] have pointed out that in pseudo-hypoparathyroidism there is a tendency to shorter stature, shortening

of the long bones and metacarpals, and a greater incidence of metastatic calcification and mental deficiency. Fortunately, both of these diseases respond to therapy with dihydrotachysterol.

Treatment

The treatment of idiopathic hypoparathyroidism consists of measures to increase the serum calcium and, if necessary, to reduce the serum phosphorus. Maintenance of the serum calcium level within normal range is of primary importance for the prevention of cataracts and the control of tetany. The cornerstone of therapy is the administration of large doses of oral calcium. This can be accomplished by mixtures of calcium lactate and calcium carbonate powder, whereas the commercial wafers of dicalcium phosphate are totally ineffective in any practical dosage range. The calcium powder in doses of five to ten drams is dissolved in approximately one quart of boiling water, and the solution is taken in four divided doses each day. The serum phosphorus level is of lesser importance except for its indirect effect on calcium metabolism and the serum calcium level. Reduction of the phosphate concentration within the intestine promotes a favorable effect on calcium absorption. The serum phosphorus can be partially controlled by dietary measures and the administration of aluminum hydroxide to increase phosphorus excretion in the stool.

Large doses of vitamin D or dihydrotachysterol, which is often more effective, are prescribed with the supplemental calcium salts. The major action of dihydrotachysterol is to promote phosphorus diuresis and its secondary effect is to increase calcium absorption from the gastrointestinal tract. Vitamin D primarily increases calcium absorption in hypoparathyroidism. Although parathyroid hormone is true replacement therapy, it is not used because it is ineffective over long periods of time due to the development of antihormones. In addition, parathyroid hormone is expensive and requires parenteral administration.

SUMMARY

A case of idiopathic hypoparathyroidism is reported, and the clinical features and treatment of the disease are reviewed.

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VALUE OF KVEIM TEST AS A DIAGNOSTIC MEASURE IN SARCOIDOSIS

A Preliminary Report

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IN 1941, Kveim[1] published a report on a "new and specific cutaneous reaction in Boeck's sarcoid." He observed that following the intracutaneous injection of a tissue suspension of sarcoid lymph nodes in 13 patients with active sarcoidosis, 12 developed a papule at the site of injection. Histologically, these papules resembled cutaneous sarcoidosis. No papule developed in patients with either tuberculosis or syphilis who were similarly tested.

The test is not widely used, however, due to a number of inherent difficulties. The sarcoid tissue is not easy to obtain in quantity. The suspension cannot be standardized as to its potency, and the length of time needed to interpret the test tends to lessen its practical application. Further, subsequent investigators have questioned Kveim's opinion as to the test's specificity. It has been claimed that dead tubercle bacilli,[2] BCG vaccine,[3,4] normal spleen suspension,[5,6] and leukemic lymph node suspension[7,8] may give a response similar to the sarcoid-tissue suspension when injected into patients with sarcoidosis. Also, the test has occasionally been reported as positive in conditions other than sarcoidosis.[7-9] Nevertheless, interest in the test has been maintained by other reports[10-18] that tend to substantiate the usefulness of this delayed papular response in the diagnosis of sarcoidosis. The Kveim test has been employed extensively at the Cleveland Clinic for the past three years. The present study is concerned with an evaluation of the test based upon the reactions in 88 patients. The results have proved to be of such consistent diagnostic and prognostic value as to prompt this preliminary report.

METHODS

Method of Preparation of the Antigen.** Portions of lymph nodes (usually cervical or axillary) are obtained at the time of surgery from a patient undergoing a diagnostic biopsy for suspected sarcoidosis. The lymph nodes are tested for sterility, and then stored in the refrigerator at about minus 10 degrees C. If the tissue is sterile and the clinical and pathologic criteria of sarcoidosis are established for the patient, it is pooled with lymph nodes similarly obtained from other patients. The pooled tissue is then ground, while frozen, in a sterile mortar. Physiologic saline is added during the grinding in the propor-

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** *Mr. Alfred Reich of the Department of Clinical Pathology has prepared all antigen used. The method described by Kveim has been slightly modified.*

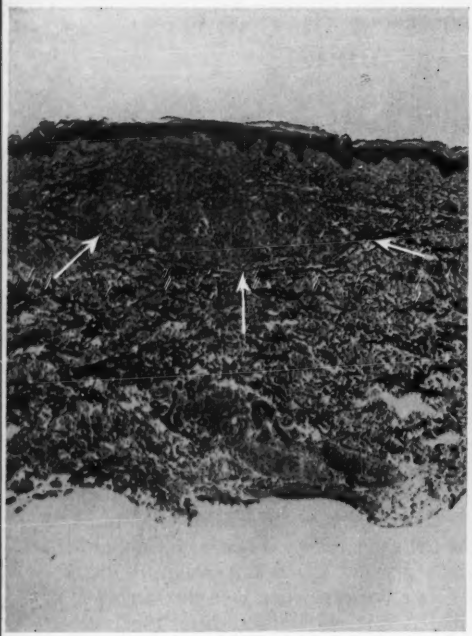

Fig. 1

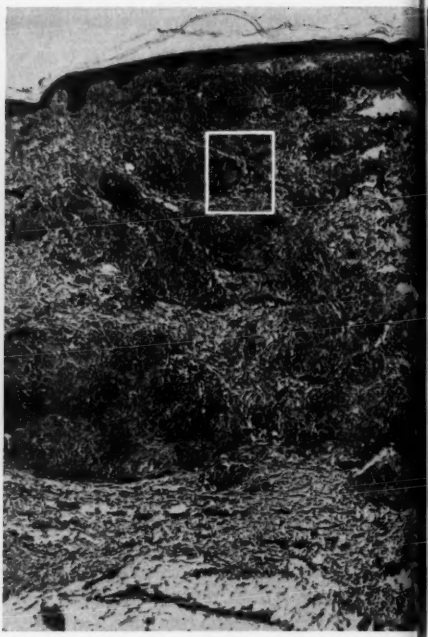

Fig. 2

Fig. 1. Positive Kveim test at six weeks. The tuberculoid reaction in this test was quantitatively small and superficial. X 35.

Fig. 2. Positive Kveim test at six weeks. The tuberculoid reaction is extensive, involving most of the dermis. Otherwise it is similar to the reaction in figure 1. X 35.

tion of nine parts saline to one part frozen tissue, by weight. Aqueous merthiolate to make a 1:10,000 solution is added as a preservative. The resultant suspension is strained through eight to ten layers of wet gauze and stored in 10 cc. vials. After pasteurization in a water bath at 60 degrees C. for one hour on two consecutive days, a final check for sterility is made. If the suspension is sterile, it is then ready for use.

Method of Testing. The suspension settles on standing and should be shaken lightly prior to use. The test is done in the same manner as is a tuberculin test: with a 25-gauge needle, the suspension is injected as superficially as possible into the dermis. With the 10 per cent lymph node suspension used, 0.1 cc. of suspension is injected. The injection is usually made on the flexor aspect of the forearm, and a mole, scar, or other landmark is used to chart the test site. Patients are instructed to return in six weeks, at which time the test site is excised with a small 5-mm. cutaneous punch.

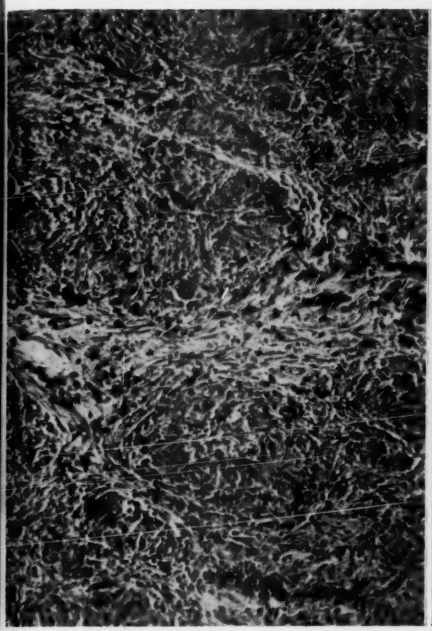

Fig. 3

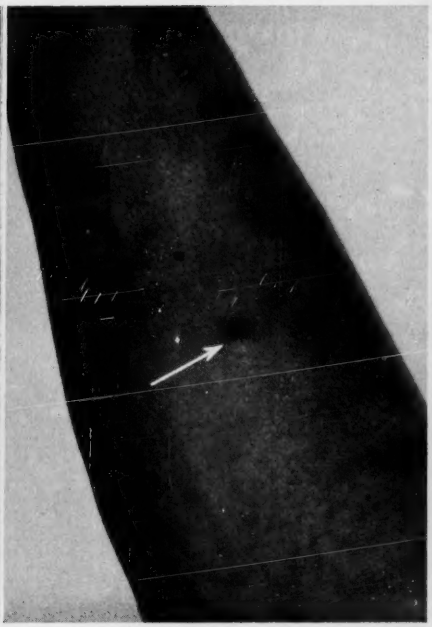

Fig. 4

Fig. 3. Enlargement of the square marked on figure 2. The tuberculoid reaction resembles that seen in sarcoidosis. X 135.

Fig. 4. Papule at site of a positive Kveim test of six weeks' duration (flexor aspect of the forearm). All papules are not this large or prominent. The size of the papule corresponds to the amount and depth of the underlying tuberculoid reaction.

EVALUATION OF THE TEST

Criterion of a Positive Test. In this study the sole criterion of a positive test is the histologic demonstration in the excised test site of a tuberculoid reaction resembling cutaneous sarcoidosis. This reaction consists of the focal collections of epithelioid cells with a variable but usually slight lymphocytic infiltration, and an occasional giant cell of the Langhans' type.

Variations in the histologic reactions of positive tests in this investigation have been thought due to three factors: (1) the differences in quality (potency) of the antigen used; (2) the differences in duration of the tests; and (3) the patient's susceptibility to the stimulus.

By preparing a large amount of antigen at one time, and injecting a constant amount for each test, the first factor is minimized as much as possible. The duration of the test prior to excision also influences the resulting histologic

characteristics of the positive test. If excised under four weeks the tuberculoid nature of the infitrate may be too immature to recognize, while if excised after three months, the test may be histologically indistinguishable from cutaneous sarcoidosis.

It has been observed, however, that tests of the same duration using the same batch of antigen will vary somewhat in their microscopic characteristics from patient to patient. Some patients will develop only a few focal areas of epithelioid cells, while others will develop a more massive reaction involving the entire width of the dermis down to and including the upper hypoderm. Figures 1, 2, and 3 illustrate the variations that have been observed in tests of six weeks' duration, using the same batch of antigen.

Other Factors to Consider in Evaluating the Test. In some reports, emphasis is placed on the cutaneous response at the test site. With a positive test, a characteristic papule usually develops which lasts for months and usually involutes in about a year. This reliance on the clinical appearance of the test site has many disadvantages however. An inflammatory nonspecific response to the antigen may develop and the resulting papule may appear similar to that produced by the true positive granulomatous reaction; or the granulomatous reaction may be quantitatively slight without the development of a well-defined papule at the test site. Much confusion has undoubtedly been created in the past by the use of poorly defined clinical criteria in assessing the test.

In this study, two patients each presented, at six weeks, a palpable infiltration at the test site, without the development of a visible papule. Microscopically, the tuberculoid reaction was situated deep in the dermis and was quantitatively small. (Early in the investigation large-bore needles were used for the injections, which, inadvertently, were occasionally given too deep in the dermis.)

At the sites of the other positive tests, papules were present. These papules began to develop as early as one week, and by six weeks had attained a size of 3 to 6 mm. in diameter. They were of a reddish-brown color, remained stationary in size up to the time of excision, and did not break down or ulcerate (fig. 4).

However, papules have developed at the test site in three instances using the suspension of sarcoid gland, and two instances using a suspension of normal spleen. Such papules appeared similar to those usually seen at the site of a positive test, but histologically revealed a mild inflammatory infiltrate without a tuberculoid reaction and these tests were considered negative.

It has also been observed that if the injection is made superficially in an area where there is little underlying fat, such as the forearm, and no papule or palpable infiltration is present at the test site within six weeks, such a test site will reveal normal skin when excised. The smallest degree of tuberculoid infiltration encountered in the present series has reflected its presence clinically as an area of induration at the test site.

All papules and test sites with the slightest suspicion of an infiltration were excised, and a positive test was interpreted solely on the basis of the histologic appearance. Also, after the excision of many "clinically negative" test sites only to find normal skin microscopically, it seems justifiable to interpret a test

as negative when no infiltration appears at the test site six weeks after the superficial injection of an antigen known to be potent.

VALUE OF THE TEST IN THE DIAGNOSIS OF SARCOIDOSIS

Patients included in this study may be divided into three groups: (1) a control group in which the diagnosis of sarcoidosis had been established before the time of the test; (2) a control group in which diseases other than sarcoidosis were present; and (3) a group in which the diagnosis was uncertain at the time of testing. In the latter group, sarcoidosis, tuberculosis, certain occupational diseases of the lungs, pulmonary malignancy, and Hodgkin's disease and other lymphoblastomas were among the diagnoses considered when the patients were first seen; in most instances the diagnoses were established only by prolonged observation, extensive laboratory investigations and/or biopsies of the affected tissues (such as lung, lymph node, liver, and skin). Group 3, in short, represents the difficult diagnostic problems in which a reliable test for sarcoidosis would be of greatest value.

A total of 88 patients have been tested and sufficiently followed to include in this study. Table 1 lists the diagnoses of these cases. They will be discussed according to the test results.

TABLE 1

Diagnoses in 88 Cases

No. of Cases	Results of Kveim Test	Biopsy of Test Site	Diagnosis	Comment
40	Positive	Yes	Sarcoidosis	Clinically active as judged by follow-up
(4)	Positive when first tested, then later negative	Yes	Sarcoidosis	(Included in group of positive tests) Retest was negative when in clinical remission as judged by follow-up
4	Negative	Yes	Sarcoidosis	3 in remission 1 entering remission
3	Negative	Yes	Sarcoidosis (?)	2 suspected sarcoidosis in active stage 1 suspected case entering remission
19	Negative	Yes	Pulmonary berylliosis—2 cases Tuberculous adenitis Interstitial pneumonitis Chronic uveitis, unknown origin Regional enteritis	Positive patch tests and work histories Positive culture

Table 1 (*Continued*)

No. of Cases	Results of Kveim Test	Biopsy of Test Site	Diagnosis	Comment
			Diffuse pulmonary fibrosis	Biopsy of lung
			Chronic ulcerative colitis	
			Mycosis fungoides	
			Chronic periostitis of nasal bones	Biopsy nasal bones
			Congestive heart failure	
			Chronic nonspecific lymphadenitis	Gland biopsy
			Rheumatic fever with erythema nodosum	
			Sjögren's syndrome	
			Pulmonary fibrosis—2 cases	Lung biopsy
			Pulmonary fibrosis with lipid pneumonitis	Lung biopsy
			Chronic parotitis (unilateral)	Gland biopsy
			No disease	
2	Negative	No	Sarcoidosis—2 cases	Patients in long clinical remission
18	Negative	No (clinically negative test sites at 6 weeks)	Pulmonary tuberculosis—9 cases	Sanatorium patients
			Tuberculous adenitis	Positive culture
			Pulmonary fibrosis	Lung biopsy
			Lupus erythematosus	
			Mycosis fungoides	
			Pulmonary berylliosis	Positive patch tests and work histories
			Emphysema	
			Regional enteritis	
			Bronchogenic carcinoma	Lung biopsy
			Chronic interstitial pneumonitis	Lung biopsy
2	Borderline (see text)	Yes	Erythema nodosum (bromides?)	Papules present at test sites when excised in 6 weeks
			Erythema induratum (?) (Darier-Roussy sarcoidosis)	

Patients Having Positive Kveim Tests. The tests were positive, by the single criterion mentioned, in 40 patients, and in all 40, diagnoses of active sarcoidosis were made independently of the tests. Table 2 lists some of the features of the group as determined up to the time of excision of the test sites. Table 3 indicates the durations of the tests prior to excision.

Data on 40 Patients Who Had Positive Kveim Tests

Race	No. of Cases	Age		Skin Lesions			Diagnostic Biopsy Performed (Lung, Lymph Nodes, Liver, Skin, etc.)
		Under 40	Over 40	Superficial Plaques	Deep Nodules	Erythema Nodosa	
White	24	19	5	1	3	3	11
Negro	16	14	2	—	4	—	8

Race	Roentgenogram of the Chest				Peripheral Lymph-adenopathy	Extensive Tuberculous Investigation
	Enlarged Nodes Only	Parenchymal Lesions Only	Enlarged Nodes and Parenchymal Lesions	Normal Chest		
White	16	1	7	—	5	6
Negro	9	1	5	1	7	6

Race	Symptoms			Estimated Duration of Disease When Tested				Tuberculin Sensitivity			Disease Found by Survey Chest X-ray
	Primarily Pulmonary	Systemic	None	Over 5 yr.	1-5 yr.	Under 1 yr.	Not Known	+ to P.P.D. 0.005 mg.	− to P.P.D. 0.005 mg.	Not Known	
White	5	8	11	4	7	8	5	1	10	13	8
Negro	1	11	5	2	5	3	6	1	9	6	1

TABLE 3

Durations of Positive Tests Prior to Excision

Time of Excision of Test Site	No. of Patients		
	White	Negro	Total
In the 4th week	1	0	1
5th	1	1	2
6th	9	5	14
7th	4	3	7
8th	3	2	5
9th	1	0	1
10th	1	1	2
11th	0	2	2
12th	1	1	2
Over 12 weeks	3	1	4
TOTAL	24	16	40

The cases in this group include a wide range of clinical types of sarcoidosis of varying degrees of acuity and causing varying degrees of disability. Some cases presented many of the classic features of the disease including splenomegaly, leukopenia, elevated serum globulin, generalized lymphadenopathy, and cutaneous lesions. Three patients (white women) were acutely ill with uveoparotid fever when tested. At the other extreme were several patients who were completely asymptomatic, without abnormal physical or hematologic findings, but with abnormal findings on x-ray examination of the chest (hilar gland enlargement). The disease was discovered in nine such patients following routine x-ray examinations of the chest; in follow-ups of these patients it was found that either they developed other manifestations of the illness, or they experienced a remission of the disease as evidenced by clearing of the abnormal pulmonary shadows.

Patients Having Negative Kveim Tests. The tests were initially negative in 46 patients. Four patients, who previously had developed a positive test, were retested when the disease entered a clinical remission (spontaneous remission in two patients and related to treatment in two others). On retesting, no reaction developed at the test sites either clinically or histologically.

Five patients with previously active sarcoidosis were tested while in remissions of six months' to five years' duration, and the tests were negative. One patient with established sarcoidosis and one with suspected sarcoidosis were tested while entering a remission, as judged by clinical follow-up and x-ray examination. The tests were negative. In two patients with apparently active sarcoidosis the tests were negative. In one of these, biopsy of the lung was only suggestive of sarcoidosis.

Of the remaining 37 patients, some were known to have diseases other than sarcoidosis when tested (control patients) and the others proved, after completion of investigative studies, to have diseases other than sarcoidosis. Two of these patients each developed a papule at the test site, but serial section of the entire excised lesion in each case failed to reveal a tuberculoid reaction. Thirty-five

patients failed to develop a reaction at the test site. Seventeen of these "clinically negative" test sites were excised and revealed normal skin. Eighteen were not excised, but the tests were considered negative on clinical grounds.

Borderline Reactions. In the majority of test sites, the histologic reaction was distinct. The tuberculoid characteristics of the positive Kveim test were readily recognized, while negative tests usually revealed normal skin or a mild inflammation. Two cases were seen in each of which the infiltrate, while chiefly lymphocytic, had, in some areas, a poorly defined, questionable tuberculoid reaction (fig. 5). They had, in essence, more reaction than the usual negative test, but did not have a sufficient or clear-cut tuberculoid response as that found in the usual positive test. Neither patient had sarcoidosis as far as could be determined.

It is reasonable to expect a certain proportion of nonspecific and atypical reactions in a test dependent on the response to injection of a foreign substance. It is therefore surprising that in the present study these reactions that are so difficult to classify have been the exception rather than the rule.

Control Antigens. Normal lymph node and normal spleen suspensions were prepared in the same manner as was the Kveim antigen. There were no

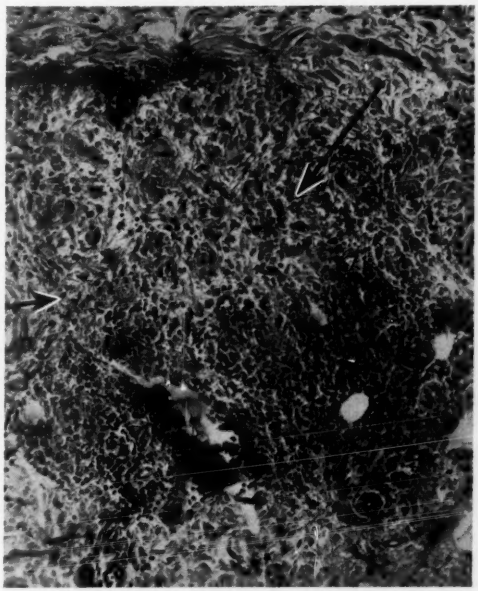

Fig. 5. Borderline reaction (see text). Poorly defined epithelioid cell and lymphocytic response to the antigen. Such responses have been quantitatively small and granulomatous in appearance but do not resemble sarcoidosis. X 135.

clinical or histologic reactions to the injection of normal node suspension in 11 patients who developed positive reactions to the sarcoid node suspension. Under similar circumstances, normal spleen suspension gave no reaction in three cases, while in two others, a small infiltration was present at six weeks, which histologically revealed a mild inflammatory infiltrate.

DISCUSSION

The results of this study support the original opinion of Kveim[1] and the subsequent experience of Danbolt[10-12,15] that the test is useful in the diagnosis of sarcoidosis. It seems preferable to base the interpretation of a positive test solely on the histologic reaction rather than on the evolution of the resulting cutaneous lesion as suggested by Danbolt.[15] By the histologic criterion, false positive papules are detected early, and the atypical positive reactions with long latent periods that have been reported in certain tuberculoderms[9] would be considered negative.

The results of the present investigation would suggest that the presence of a tuberculoid reaction resembling sarcoidosis at the Kveim test site in six weeks (i.e. a positive test) is strong evidence that the patient has active sarcoidosis. The absence of such a reaction (assuming the antigen is potent) would suggest that the patient either does not have sarcoidosis, or that the proliferative phase of sarcoidosis is in remission.

There have been no cases of delayed papules in the present series. If the test was clinically negative at six weeks (i.e. no papule or palpable infiltration at the test site) it remained negative in the few cases in which the test site was not excised.

The scars following the excision of positive and negative tests have been normal. No instances of an untoward local reaction either before or after excision have been encountered in this study.

The lack of response to a suspension of normal lymph nodes is generally agreed upon by all investigators. This investigation, as well as Danbolt's, has been unable to confirm the report that normal spleen suspension produced reactions similar to those produced by the sarcoid-tissue suspension.

Two of the patients with active sarcoidosis had positive tuberculin tests. The results of the Kveim test in these two were in no way different from the results in the tuberculin negative group with active sarcoidosis.

SUMMARY

Kveim tests were performed on 88 patients. The tests were positive in 40 patients, all of whom had sarcoidosis in a clinically active phase. In four of these, a second test was negative when the disease entered a remission.

The tests were initially negative in six patients with sarcoidosis in a remission or entering it; in two patients with suspected sarcoidosis in a clinically active

phase; in one patient with clinically active sarcoidosis entering a clinical remission; and in 37 patients with other diseases.

The tests were difficult to interpret in two patients.

The majority of the test sites were excised in the sixth, seventh, or eighth week.

A positive test was based on the histologic demonstration in the excised test site of a tuberculoid reaction resembling sarcoidosis.

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ERRORS IN SURGERY OF THE BILIARY TRACT*

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The Incision

IT has been said by generations of surgical teachers that abdominal wounds heal from side to side and not from end to end. The implication is that it makes no difference how long the incision is, so long as it gives adequate exposure.

Any abdominal incision, if long enough, affords good exposure. But is it really true that the length of the incision makes no difference to the convalescence of the patient? By reductio ad absurdum it is obvious that an incision 1 inch long would give less chance of wound disruption, hernia, hematoma, and infection than one 18 inches long. How long an incision can one make without increasing the incidence of these complications? Statistics on the subject are not available, but it is amazing and a little frightening to see the high incidence of hernias in the scars of upper abdominal operations. Since hernias are incomplete wound disruptions, the incidence of complete disruptions with their attendant mortality must also be significant.

The first consideration in all surgery is exposure, and no one will argue that this prerequisite of an accurate operation should be jeopardized by a keyhole incision. On the other hand, both the exposure afforded and the strength of the closure depend as much on the type of incision made as on its length. Most gallbladders lie fairly far lateral, away from the line of a right rectus incision. Adequate exposure of the gallbladder can be obtained by retraction, if the incision is long enough, but through a much shorter subcostal incision comparable exposure of both gallbladder and common duct is obtained and the strength of the closure, as in all oblique or transverse incisions, is considerably greater.

Since technics of abdominal closure vary, and a method that is successful in the hands of one surgeon may fail in those of another, a single surgeon's experience is not necessarily representative of the over-all experience of the profession. Nevertheless, in my own hands the incidence of postoperative hernia and wound disruption has been much less when abdominal incisions have been closed not with catgut but with interrupted, figure-of-eight, stainless steel sutures, and it is even lower when subcostal or transverse incisions are employed.

Injuries of the Hepatic Artery

Injuries of the bile ducts rank high among the complications of biliary surgery, yet it is quite possible that injuries to the hepatic artery are even more common. In the Navy, I had considerable experience in assisting inexperienced

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surgeons in cholecystectomies, and was surprised to find that the most frequent serious mistake from which they had to be directed was not injury of the common duct but ligation of the hepatic artery. When a tortuous hepatic artery loops up to the gallbladder and gives off only a tiny cystic branch, it is easy to mistake a small hepatic for a large cystic artery.

If the hepatic artery is ligated in some cases there may be no untoward sequelae but in others the patient may die with high fever, urinary suppression, jaundice and shock. This syndrome, resulting from necrosis of liver substance and perhaps from the multiplication of anaerobic organisms, is not always recognized to be the result of damage to the artery, and perhaps some deaths attributed to renal or liver failure are in reality the result of this accident. It can be prevented by:

1. Never ligating fat and peritoneum in mass without dissecting out their component parts.
2. Never ligating a large cystic artery until it has been traced upward and its branches on the gallbladder demonstrated.
3. In doubtful cases, dissecting from the fundus down, and ligating *only* on the wall of the gallbladder.

Injuries of the Common Duct

In the surgical literature there is much implied criticism of surgeons who injure the common duct during cholecystectomy. Sometimes this criticism is just, for the accident can result from carelessness. The fact that many of the injuries occur in thin patients with uncomplicated chronic cholecystitis rather than in the difficult cholecystectomies done for acute or subacute cholecystitis indicates that it is the "easy case" that may tempt the surgeon to proceed rapidly with insufficient attention to detail. It is in this same type of case that a very short cystic duct pulls up a loop of common duct so that if the common duct is small it may be divided before it is recognized.

Sometimes, however, even when the greatest care is employed, ducts accidentally may be injured. I remember a slender young woman in her thirties with an uncomplicated cholecystitis. Exposure was excellent. At the base of the gallbladder I picked up a small duct no bigger than a normal cystic duct and followed it down into the gastrohepatic omentum looking for its junction with the common duct. I could not find the junction. Realizing that there was an anomaly of the duct system, I removed the gallbladder carefully from above downward. At the completion of the dissection, the duct that I had originally found was seen to lead directly from the bottom of the gallbladder into the gastrohepatic omentum.

A cholangiogram showed that diatrast injected into the duct entered the duodenum promptly but showed no communication with the radicals of the

biliary tract. There were only two ties in the gallbladder bed, one on the pulsating cystic artery and the other on a tiny structure the size of a match stick which I had interpreted as an accessory vessel or accessory cystic duct. I removed the tie from this, and bile flowed from a tiny hole in the liver. A cholangiogram of this sinus showed the hepatic duct system: tiny hypoplastic ducts not one-third their usual size. It was with the greatest difficulty that this duct was dilated to admit the smallest T tube and was then anastomosed to the equally small lower end of the common duct.

This case was deeply disturbing to me, because it showed that even in the presence of a recognized anomaly of the cystic duct and with the most careful dissection of which I was capable, it was possible for me to injure a hypoplastic and anomalous common hepatic duct. On still another occasion I have seen a gallbladder with no cystic duct and with the common hepatic duct entering one side of the bladder and the common duct leaving from the other in such a way that complete removal of the gallbladder would lead inevitably to injury of the duct. In view of these observations I cannot feel too critical of those who have injured anomalous ducts. I do believe, however, that the majority of accidents should be recognized and the damage repaired at the time of the cholecystectomy, and that if the surgeon is constantly aware of how easy it is to injure a duct, he will double check the anatomy of the common and hepatic ducts before closing the abdomen. His attitude, when things do not seem right, should not be: "It is impossible for this to have happened to me, everything must be all right regardless of how it looks." Instead, it should be: "It is perfectly possible for any surgeon to injure a duct and until I prove to myself that I have not injured it, I must assume that I have."

Role of Cholangiography

One of the best ways to evaluate the anatomy of the biliary tract is by operative cholangiography. Anomalies, stones, and obstructions due to pancreatitis or to tumors can be visualized clearly. The technic is simple and if properly executed does not add more than five minutes to the operating time. Injuries of the common duct would largely be avoided if cholangiograms were performed routinely before gallbladders were removed. Cholangiography is at least as accurate as exploration in determining the presence or absence of stones. Its routine employment at the time of cholecystectomy saves many needless explorations of the common duct and the attendant increase of morbidity and hospitalization.

Cholangiography is not one hundred per cent accurate and a normal appearing cholangiogram should not be interpreted as conclusive evidence that stones are not present. If there are clear-cut indications, such as a history of jaundice or a dilated cystic duct with small stones in the gallbladder, the common duct should be explored regardless of the cholangiogram. The accuracy either of

cholangiography alone or of exploration alone may be approximately 90 per cent, but the combination of the two methods increases the accuracy to nearly 100 per cent. Clinical indications of stones should therefore remain as clear indications for both cholangiography and exploration.

Cholangiography performed after the common duct has been opened is never as accurate as when it is done through the cystic duct before there is any possibility of air bubbles entering the duct system. Nevertheless, even after exploration, if the duct has been irrigated and barbotaged with water and if all air has been aspirated before the cholangiogram is made, air bubbles do not often cause confusing negative shadows. Certainly in all cases in which multiple stones have been removed, exploration should be followed by cholangiography. The necessity of this procedure was emphasized by a recent case in which careful exploration of the duct with scoops, catheters, and lavage had recovered 29 stones. I was certain that the duct system was clear, but before closing the abdomen we took a postexploratory cholangiogram. Three negative shadows were present, and on re-exploration I found out what had happened: I had been pushing the three stones into the short dilated stump of the cystic duct which trapped them like a diverticulum, as I withdrew the probe. Later they fell back into the common duct. After removing the three stones, cholangiograms showed the duct to be clear.

Operations on the Ampulla of Vater

In recent years much has been written about spasm of the sphincter of Oddi, and about pancreatitis occurring in the presence of a common opening of the pancreatic and common bile ducts. The pioneers in this field have perfected technics of sphincterotomy which in their hands are reported to be safe and satisfactory, but end results in these conditions require years to evaluate. Occasionally any operation or even a strong suggestion causes prolonged improvement in the typically anxious or hysterical type of patient who develops the postcholecystectomy syndrome. Sphincterotomy is not an easy operation, and in my experience it has been accompanied by a high morbidity and occasionally by fatal pancreatitis. For this reason it is not to be undertaken lightly, or as a routine measure just because cholangiography shows a common opening or evidence of sphincter spasm. Diseases of the biliary tract should be treated first, and theoretical disorders of the sphincter mechanism and of the pancreas disregarded until the results of the biliary tract operation have been assessed. If symptoms persist, after stones and obstructions of the biliary tract have been treated, the problem of the sphincter of Oddi should be considered and if operation is to be done it should be by a surgeon who has a particular interest and technical experience in this difficult and dangerous field.

SUMMARY

The most serious errors in surgery of the biliary tract involve complications of closure of the incision, injuries to the hepatic artery and common duct, and residual stones in the common duct. Technical errors should be corrected and repaired at the time of the primary operation. Operative cholangiography is a valuable adjunct to surgery of the biliary tract. The problems of chronic pancreatitis and spasm of the sphincter of Oddi have not as yet been satisfactorily solved.

REGIONAL ENTERITIS INVOLVING THE DUODENUM

Report of Two Cases

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REGIONAL enteritis is a disease with diverse and protean manifestations that may simulate those of many other gastrointestinal conditions. Although the terms "terminal ileitis" and "regional ileitis" have been used as synonyms for "regional enteritis," they are misleading for the disease is not limited to the terminal ileum but may involve any segment of the small intestine and portions of the colon. The disease frequently involves the small intestine with "skip areas" of inflammation with normal intestinal mucosa between the involved segments. Comfort and associates[1] have suggested that the condition be termed "nonspecific granulomatous gastroenteritis," but this vague term merely emphasizes the fact that little has been added to our knowledge of regional enteritis since Crohn's[2] original description of its etiology and pathogenesis in 1932. "Regional enteritis" remains the most widely accepted name for this condition.

Regional enteritis involves the terminal ileum in 75 per cent of the cases. The frequency of involvement of a specific segment is directly related to its proximity to the ileocecal valve; however, isolated cases of enteritis occurring high in the jejunum have been reported. Involvement of the duodenum, a relatively short segment, is unusual; there are only 13 reports[1,3-7] of such cases in the literature. Although some of the reported cases are not described histopathologically, all of them must be considered as nonspecific, granulomatous, cicatrizing inflammation of the uppermost intestinal tract (duodenum), because of the clinical characteristics and the surgical descriptions of the pathology.

Comfort[1] reported a typical clinical picture presented by patients having regional enteritis involving the duodenum. He found that symptoms could be classified into four categories: (1) Continuous and intermittent upper abdominal distress intensified by food, loss of weight and strength, nausea and occasional vomiting; (2) Diarrhea, steatorrheal and episodic in type; (3) Gastric retention, denoted by succussion splash and by morning aspiration of greater than normal amounts of gastric contents (and, if we may add, the vomiting of food particles eaten as much as eight hours previously); and (4) Evidence of deficient absorption. Many of these symptoms are due to a high partial obstruction and are not specific for regional enteritis. We have seen all of them, including diarrhea, in patients with mechanical obstruction of the upper jejunum. Yet, cases of regional

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enteritis involving the duodenum should not go unrecognized and they should never be erroneously labeled as functional disease.

Two case reports of patients having regional enteritis involving the duodenum are presented because of the rarity of the condition, the importance of recognizing it, and the peculiar symptoms that the disease produced.

CASE REPORTS

Case 1. A 34 year old woman was first seen in May 1951 at which time she complained of nausea and vomiting of one to two quarts of liquid two to four hours after the evening meal. The symptoms had been present for 12 months. Occasionally the sensation of fullness that preceded the vomiting had awakened her during the night and she had obtained relief by vomiting. There had been no pain, hematemesis, jaundice or diarrhea, and no loss in weight despite the emesis. Five months before admission a roentgen examination made elsewhere had shown a "stricture of the duodenum" and "gastric retention."

Physical examination was essentially normal: she was 62 inches tall and weighed 165 pounds with no evidence of loss of weight. Laboratory examinations, including blood count, urinalysis, stool examination, blood sugar, calcium, urea, albumin-globulin ratio, prothrombin time, serology and serum amylase, were all normal. Gastric analysis yielded 1500 cc. of fluid with a free HCl of 20 and a total acidity of 33 units.

Roentgen examination revealed the esophagus and the stomach to be normal, except there was some fluid in the stomach after 12 hours of fasting. There was gross dilatation of the first and second portions of the duodenum with marked narrowing and irregularity of the third portion suggesting ulceration (fig. 1). A long segment of the third portion of the duodenum was narrowed.

Because of the organic obstruction of the third portion of the duodenum, operation was advised. At surgery, a segmental, cicatrizing, obstructing, granulomatous lesion of the third portion of the duodenum was recognized. On abdominal exploration, the remainder of the small intestine was normal, with no evidence of enteritis involving any other segment of bowel. A duodenojejunostomy was done, anastomosing in a side-to-side, antecolic, iso-peristaltic fashion the second portion of the duodenum and the jejunum 8 inches distal to the ligament of Treitz. Biopsy of the duodenum showed chronic inflammation in the mucosa and muscularis mucosae.

The patient had an uneventful postoperative course with complete relief of symptoms. A well-functioning duodenojejunostomy was demonstrated by roentgen examination and she was discharged from the hospital 13 days after the operation. She has remained entirely asymptomatic for the two and one half years since surgery.

Summary. A patient, whose only complaint was a retention type of vomiting for 12 months, was found by roentgen examination to have an obstructing lesion of the third portion of the duodenum. At operation a segmental, cicatrizing, obstructing lesion was revealed. A duodenojejunostomy was done and has given complete relief to the patient for the two and one half years since the operation.

Comment. Repeated daily vomiting of large quantities of food without loss of weight frequently is regarded as having functional origin. This case

Fig. 1. (Case 1) Constant deformity and narrowing of the third portion of the duodenum with dilatation of the proximal duodenum. Some irregularity of the narrowed third portion of duodenum.

demonstrates that such vomiting due to an organic lesion may occur without causing any loss of weight.

In connection with obstructive lesions of the duodenum and upper jejunum distal to the mid-second portion of the duodenum, there is one point concerning the choice of operation about which we could find little discussion in the literature. In cases such as case 1, it would seem that a duodenojejunostomy is indicated rather than a gastrojejunostomy. If there is a complete duodenal obstruction distal to the ampulla of Vater, and a gastrojejunostomy has been done, the alkaline pancreatic juices and bile can gain access to the small intestine only by regurgitation through the stomach. If instead, a duodenojejunostomy has been done, the alkaline bile and pancreatic juices can gain ready access to the small intestine through the anastomosis. Thus, if the cicatrizing process approaches complete stenosis, the proximal portion of the small bowel receiving the acid gastric juice is not denied a direct and free supply of alkaline bile and pancreatic secretions when a duodenojejunostomy is done. In such cases, a duodenojejunostomy may result in fewer sequelae of the operation, such as distressing regurgitation of bile into the stomach and a lower incidence of marginal ulcer, than would a gastrojejunostomy.

Case 2. A 24 year old woman in October 1948 first complained of a sharp epigastric pain with radiation to both right and left upper quadrants. In addition she had complaints referable to every other system in the body characteristic of a conversion neurosis. The epigastric pain occurred once or twice a week, was of 10 to 15 minutes' duration, and was associated with nausea. Complete studies were negative except for some questionable deformity of the duodenal bulb. She was given antispasmodics and was asked to return in one month for a recheck roentgenographic examination of the stomach.

She was next seen three years later (August 2, 1951) at which time she complained of nausea and vomiting. A 30-pound loss of weight had occurred during the preceding two and one half months. For one month prior to the appearance of these symptoms she had had watery, bloody, mucous diarrhea and had experienced lower abdominal cramps. She had been married one month prior to the onset of the present illness; this was her second marriage and already it was fraught with emotional problems. She referred to her husband in uncomplimentary terms, and stated her belief that he was responsible for her illness. She was admitted to the hospital with a tentative diagnosis of anorexia nervosa.

Intravenous fluids to correct a marked electrolytic imbalance, gastric tube feedings, and finally frequent small oral feedings were given. Psychiatric consultation confirmed the diagnosis of a conversion neurosis. Because of continued vomiting despite therapy, gastroenterologic consultation was requested two weeks after admission to the hospital. An upper gastrointestinal x-ray examination showed marked gastric retention, presumably due to pyloric obstruction. Barium enema examination showed narrowing and distortion of the mucosal pattern of the terminal ileum (fig. 2).

At operation, the stomach was thick walled, edematous and dilated. The duodenum was greatly thickened throughout its first portion and rubbery firm to palpation. Its serosal surface was injected with many telangiectatic vessels and showed a loss of its normal glistening surface. The induration in the duodenal wall was diffuse, and no ulcer crater could be palpated. The induration began just distal to the pylorus and extended to the distal extremity of the first portion of the duodenum. The terminal ileum was found to be involved in a similar process and was typical of those found in cases of

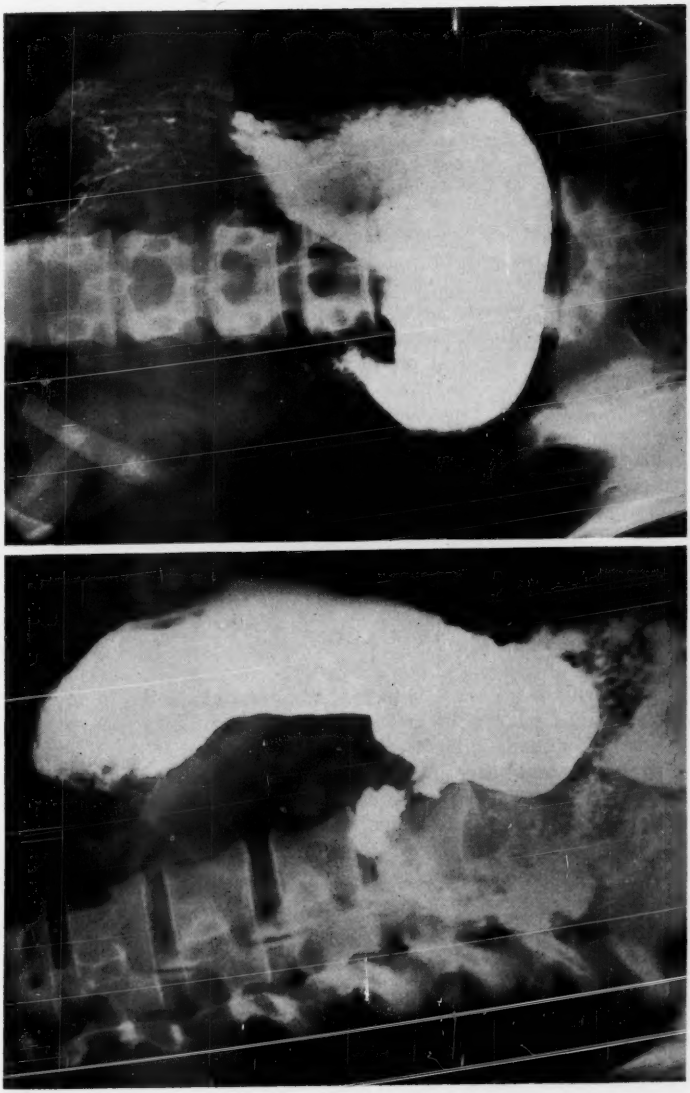

Fig. 2. (Case 2) Marked duodenal deformity. Duodenal bulb never filled out well. No ulcer crater demonstrated. Eighty per cent gastric retention in three hours.

regional enteritis. A vagotomy and gastroenterostomy was done, and since the lesion in the terminal ileum was not severe enough to cause obstruction, no resection was attempted.

The patient had an uneventful postoperative course. She gained 25 pounds in weight and felt well during the first two months after operation except for mild abdominal cramps following emotional upsets. A year after operation she requested psychiatric consultation because of extreme marital discord. Two years after operation she occasionally had loose stools two to three times a day and lower abdominal cramps. Roentgen examination of the small bowel showed no change in the terminal ileum, the distal ileum being narrowed and irregular for 4 to 5 inches.

Summary. A patient with severe emotional problems was treated for two weeks for anorexia nervosa before it was discovered that she had almost complete gastric obstruction and terminal ileitis. She improved following vagotomy and gastroenterostomy and, except for occasional mild episodes of diarrhea and lower abdominal cramps, remained relatively symptom-free for two years following surgery. Her emotional problems continued to disturb her.

Comment. This patient demonstrates quite well the fact that patients with functional disease may have organic disease as well. Before a diagnosis of anorexia nervosa is made, it is essential to rule out any possible organic gastrointestinal disease that could cause the patient's symptoms. A diagnosis of anorexia nervosa must be made not only by positive evidence of a severe psychoneurosis, as in this patient, but also by excluding any possibility of the existence of organic disease.

DISCUSSION

Regional enteritis is a disease with manifestations simulating many other pathologic gastrointestinal conditions including functional abdominal disorders. The diagnosis is frequently difficult to determine until after the disease has existed for some time and has resulted in obstruction of the small intestine. The two patients whose case reports are presented, exhibited symptoms of gastric obstruction due to regional enteritis involving the duodenum. Other symptoms more frequently present are those of diarrhea, lower abdominal pain, symptoms due to partial obstruction, and fistulae formation. Fever may be a predominant or the single symptom for a long time. We saw a third patient who had a cholecystectomy for a low-grade fever and a nonfunctioning gallbladder. She continued to have a fever after the cholecystectomy. It was not until 18 months after the cholecystectomy that she developed diarrhea, and a diagnosis of regional enteritis was established by roentgen examination and at operation.

Diarrhea is frequently present but there can be extensive regional enteritis without diarrhea. In the third patient mentioned in the preceding paragraph, the disease was present and caused a low-grade fever for at least 18 months before diarrhea developed. In cases 1 and 2 in which there was involvement of the duodenum, only one patient had diarrhea and that for only one month

before the operation. If diarrhea is a necessary symptom before one becomes suspicious of this condition, many cases will be diagnosed late in the course of the disease or never will be correctly diagnosed.

In some patients anemia may be the chief symptom and may be present for a long period before other manifestations of regional enteritis appear. This disease should be considered in the differential diagnosis of unexplained anemia. Because of the marked tendency to fistulae formation in cases of regional enteritis, we believe that the possibility of the presence of this disease should be considered in any patient with a fistula, including a perianal fistula.

Regional enteritis involves the terminal ileum in 75 per cent of the cases. Frequently the terminal ileum will be filled on barium enema examination, and it is possible to exclude many cases by this examination alone. In suspected cases of regional enteritis, we believe that a barium enema examination should be done before any x-ray studies of the small intestine. In some cases, roentgen studies of the small intestine will not be necessary. In others, barium enema examination may suggest disease of the terminal ileum which may or may not be substantiated by roentgen examinations of the small intestine.

It is frequently difficult to demonstrate disease in the small intestine by x-ray examination until that disease has become quite extensive and has caused at least partial obstruction. Of all the possible gastrointestinal x-ray studies, that of the small intestine is the least satisfactory. Therefore, in cases in which regional enteritis or other small-intestinal diseases are suspected, it may be necessary to repeat the roentgen study of the small bowel later to establish the true condition. If regional enteritis is suspected clinically despite a "normal" small bowel on x-ray examination, it is always advisable to repeat the roentgen examination after several months.

SUMMARY

Two cases of regional enteritis involving the duodenum are reported. Such involvement is rare; only 13 such cases having been previously recorded. Both patients presented symptoms of gastric or duodenal obstruction. Both were relieved by side-tracking operations, a duodenojejunostomy in one and a gastrojejunostomy in the other. The rationale of doing a duodenojejunostomy rather than a gastrojejunostomy for obstructive lesions of the duodenum and jejunum distal to the mid-second portion of the duodenum is discussed. The possibility of mistakenly considering patients with regional enteritis as having functional disease (one of the patients having been treated for anorexia nervosa for two weeks) is discussed, and the various manifestations of regional enteritis are presented. Regional enteritis should be considered in the differential diagnosis of obstructing lesions of the duodenum.

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SURGERY FOR MITRAL STENOSIS

Part II. Mortality in Mitral Commissurotomy

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EVALUATION of a new surgical procedure such as mitral commissurotomy must depend upon consideration of its total cost as compared to the benefits obtained by its use. Functional improvement due to mitral commissurotomy can now be assessed only on a short-term basis. A number of years must pass before the ultimate results of combined surgical and medical management can be ascertained. At present, the value of surgical intervention in properly selected patients with mitral stenosis appears to be clearly established.

In assessing the cost of the procedure, the mortality and morbidity involved are the primary considerations. Of these, mortality is more important and more easily defined. The first mitral commissurotomy at the Cleveland Clinic was performed in May 1951, and the 100th operation of the consecutive series in December 1953. Of the 100 patients, 92 survive. The purpose of this report is to analyze the causes of death in the early postoperative period with the aim of determining such measures as may make the operation safer in the future.

Of the eight patients, six died in the hospital after operation; two died of their disease after discharge from the hospital, one approximately two months after discharge and the other more than a year later. The cause of death in each of the six who died during postoperative hospitalization was determined by postmortem examination (table 1). The two patients who died elsewhere after discharge were not observed during the terminal phases of their illnesses. Postmortem examinations were obtained in both cases. Although the complete findings are not yet available to us, the two patients are presumed to have died of their disease.

Before this operation was undertaken, an attempt was made to anticipate the complications that might be encountered. Ventricular arrhythmias and uncontrolled hemorrhage at the time of surgery were the most feared complications but did not materialize. Death in the operating room did not occur. There was no instance of cardiac arrest or ventricular fibrillation that required cardiac massage or electroshock defibrillation. The causes of the six early postoperative fatalities can be grouped under three categories: (1) cerebral

TABLE 1

Analysis of Factors in 6 Hospital Deaths after Commissurotomy

Case No.	Sex	Age (Yr.)	Preoperative Evaluation	Operative Findings	Time of Death	Cause of Death	Postmortem Findings	Preventable or Not-Preventable	Comment
1	F.	37	Pure stenosis, fibrillation, cong. failure.	Pure stenosis. Good valvulotomy.	2nd p.o. day.	Cerebral embolus.	Embolus rt. middle cerebral artery.	Not preventable.	Occurred several hr. p.o. Occluding vessels would not have helped.
2	F.	26	Pure stenosis.	Pure stenosis. Good valvulotomy.	4th p.o. day.	Shock and tamponade, pericardial bleeding.	Pulm. edema cardiac hypertrophy.	Preventable.	Considered an error of technic.
3	F.	41	Pure severe stenosis, marked cardiomegaly, fibrillation, pulm. vascular disease.	Pure stenosis, fresh thrombus in auricular appendage. Good valvulotomy.	1st p.o. day.	Cerebral embolus.	Large mural thrombus, embolus left middle cerebral artery.	Not preventable.	Vessels occluded during surgery. No neurologic signs until several hours postoperative.

4	M.	42	Pure stenosis, left pleural effusion.	Pure stenosis. Good valvulotomy. Old pleural thickening.	10th p.o. day.	Probable cardiac arrhythmia, ? quinidine toxicity.	No significant findings.	Probably preventable.	Quinidine Rx for postoperative fibrillation.
5	M.	47	Stenosis and insufficiency, severe pulm. hypertension, auricular fibrillation, diffuse pulmonary fibrosis.	Markedly calcified valve, predominant stenosis, severe pulmonary disease. Fair valvulotomy.	11th p.o. day.	Cardio-pulmonary failure.	Severe unclassified pulmonary fibrosis.	Not preventable.	Calculated risk, pulmonary insufficiency probably chief cause of death.
6	M.	56	Pure stenosis, cong. failure, marked myocardial insufficiency.	Pure stenosis. Good valvulotomy.	15th p.o. day.	Cardio-pulmonary failure.	Purulent bronchitis, broncho-pneumonia, multiple thromboses, arterioles of lung. Empyema.	Not preventable.	Calculated risk.

embolization, (2) error in technical management, and (3) the bad-risk patient. Appreciation of the significant factors in each category may lead to a reduction in the current rate. If so, mitral commissurotomy performed under proper circumstances will have a mortality rate of perhaps 2 to 3 per cent.

1. Cerebral Embolization. Embolization has long been recognized as a frequent complication or valvular heart disease, especially in the presence of auricular fibrillation or congestive heart failure. Observations during operation have shown that thrombi commonly occur in the left auricular appendage and within the atrium and that thrombi within the right auricle and systemic veins are also common. Hence, embolization is a frequent hazard and probably will remain an unpredictable factor in mitral valve surgery. Two of our patients died of cerebral infarction due to emboli which were dislodged during or shortly after operation. Both of these patients were young women with pure mitral stenosis in whom good surgical outcomes were anticipated. Postmortem examination in each case revealed the source of the embolus to be within the left auricle at the junction of the auricular appendage.

Embolization following mitral commissurotomy is by no means confined to the brain and is not always fatal. Clinical evidence of embolization occurred in six other patients, all but one of whom have recovered without residual effects. Three of these were probably spared cerebral emboli by the technic of intermittent occlusion of the innominate and left carotid artery, suggested by Bailey.[1] This measure is designed to divert a fragment of clot or calcium to the descending aorta, and was employed as a routine measure in most patients of this series. Two emboli to the lower extremities, and one embolus to the mesentery occurred when this technic was employed and all patients recovered without further surgical intervention. In spite of all present precautions, embolism will continue to be a definite factor in operative mortality.

2. Errors in Management. The surgical care of the patient with mitral stenosis has become a well-regulated hospital procedure. Nevertheless, there are numerous details that apply solely to individual cases and offer unsuspected pitfalls. Two hospital deaths were attributable to errors in technical management. The loss of these two patients was particularly tragic, as both had had valvulotomies that promised excellent clinical results; in retrospect both deaths were avoidable. One patient, a 26 year old woman (case 2), was re-explored on the third postoperative day because of cardiac tamponade. It was thought that there was a leak in the auricular appendiceal stump. The bleeding, however, was from a small, pericardial vessel at the base of the superior pulmonary vein. It was easily ligated, but the patient did not recover. Failure to insure adequate hemostasis at the time of valvulotomy is a surgical error.

The second patient, a 42 year old man (case 4), had a technically satisfactory operative procedure. On the fifth postoperative day, he developed auricular fibrillation. After his ventricular rate was controlled with digitalis, gradually increasing doses of quinidine were employed in an attempt to restore sinus rhythm. On the ninth and tenth days after operation, he received 0.6 Gm. of

quinidine sulfate every four hours. He died unexpectedly in his sleep during the night of the tenth postoperative day, and postmortem examination demonstrated no apparent cause. It is assumed that his death was due to ventricular fibrillation, precipitated by quinidine. The incrimination of quinidine in this case is purely presumptive as no evidences of quinidine intoxication were recognized. The drug had been used frequently before and has been used since without difficulty. Of 49 patients with sinus rhythm before operation, 25 have developed auricular fibrillation during the early postoperative period. It has been possible to restore normal sinus rhythm in 22 of these patients. In every instance, successful treatment was accomplished by the use of procaine amide, quinidine, or a combination of the two drugs.

3. The Bad-Risk Patient. Selection of the surgical candidate may be hazardous in any new surgical procedure. There are seriously ill patients with rheumatic heart disease to whom all medical therapy had been offered and has failed and whose surgical indication is desperation itself. In most of these, disability is due to a combination of factors rather than to mitral stenosis alone. Myocardial damage, associated valve deformities, and superimposed pulmonary disease are formidable in the surgical candidate. Obesity, malnutrition, and arteriosclerosis also are important factors in estimating the individual's ability to recover from operation. When adequate and prolonged medical management is incapable of resolving all objective manifestations of congestive heart failure, at least temporarily, the patient is not considered a candidate for surgery.[2]

There are, however, other patients who are not obviously disqualified. These may show 40 to 60 per cent cardiac enlargement, very severe pulmonary hypertension, and pulmonary fibrosis and emphysema, but respond to medical measures by resolution of the signs of heart failure. When such patients have mechanically severe mitral stenosis, they may be greatly benefited by mitral commissurotomy. This series includes a number of these, of whom two died. Most of those who survived have shown surprising recovery and effective rehabilitation. These two deaths occurred in men, aged 47 (case 5) and 56 years (case 6), who were accepted for surgery as calculated poor risks. The hazard was explained in detail to the patients and to their families. Both patients were given prolonged preparation in the hospital before surgery, and both demonstrated sufficient improvement in their over-all status to brighten an otherwise gloomy prognosis. In each case, the immediate postoperative course was difficult, but serious trouble was not encountered until the end of the first week.

On the eighth postoperative day, the one patient (case 5) became progressively dyspneic with prolongation of the expiratory phase of respiration and the development of moderate cyanosis. He presented the clinical picture of intractable bronchial asthma with progressive anoxia. Death occurred on the eleventh postoperative day. There had been no evidence of pulmonary edema or of increasing systemic congestive changes. There had been no major bronchial

obstruction by mucous plugs, such as is frequently encountered in patients who are unable to cough up bronchial secretions in the first few postoperative days. Postmortem examination revealed extremely severe chronic pulmonary disease, characterized by diffuse focal fibrosis of alveolar membranes, interlobular fibrosis, diffuse occlusion of bronchioles by mucous plugs, and severe generalized pulmonary vascular disease involving both the major vessels and the precapillary arterioles. We consider this pulmonary disease to be irreversible.

The sixth patient was the oldest in the entire series. In addition to long-standing congestive heart failure, which had been temporarily cleared by medical management, there was evidence of moderately severe, generalized arteriosclerosis. Postoperatively, wound healing was delayed, and on the eleventh postoperative day, he suddenly developed a pressure pneumothorax on the left. This was complicated by the development of empyema, and death occurred on the fifteenth postoperative day.

Timely recognition of the patient who will not be able to tolerate the postoperative course of mitral commissurotomy will always be a matter of individual judgment and experience. It is now obvious that neither of these two patients were suitable candidates for surgery; nevertheless, a large number of similar poor-risk patients have survived the operation and have demonstrated appreciable improvement.

SUMMARY AND CONCLUSIONS

Surgery for mitral stenosis is now an established procedure. Although its long-term benefits have yet to be ascertained, the mortality rate of this operation compares favorably to mortality rates of other types of elective major surgery. The technic is standardized, and deaths during operation rarely should occur.

In a series of 100 mitral commissurotomies performed at the Clinic between May 1951 and December 1953, eight deaths occurred, six in the early postoperative period. Causes of death in the six are analyzed and categorized.

1. Cerebral embolization. In the good-risk patient with symptomatic mitral stenosis, the greatest danger is embolization. Two patients in whom a good surgical outcome was anticipated died of cerebral infarction due to emboli which were dislodged during or shortly after operation. Three of six additional patients who manifested clinical evidences of embolization were probably spared the development of cerebral emboli by the Bailey technic of intermittent occlusion of the innominate and left carotid artery.

2. Errors in management. Although the surgical care of these patients is a well-regulated hospital procedure, two deaths were attributable to avoidable errors in technical management. One of these patients was re-explored because of cardiac tamponade. A tiny vessel in the pericardium at the base of the superior pulmonary vein was easily ligated but the patient failed to regain consciousness. The second death occurred after a technically satisfactory procedure and was probably due to ventricular fibrillation, attributable to the use of quinidine. The incrimination of quinidine is presumptive. Anticipated fatali-

ties from cardiac arrest and uncontrolled hemorrhage did not occur in this series. This may be ascribed to careful preoperative preparation, light anesthesia, and continual electrocardiographic monitoring during operation. This last precaution has made it possible to recognize potentially dangerous alterations in heart rhythm before they become apparent in the surgical field.

3. The bad-risk patient. It is not possible to be dogmatic about the selection for surgery of patients with very severe rheumatic heart disease and mitral stenosis. There are several factors, however, which influence the final decision to select or to reject the individual candidate for commissurotomy. It must be emphasized that the mechanical effect of mitral stenosis is only one factor in the production of symptoms in many patients with rheumatic heart disease. Intractable myocardial insufficiency may preclude any benefit from surgery. The patient with more than 40 per cent cardiac enlargement presents a greatly increased surgical risk, and desperation alone is not an indication for surgical intervention. The importance of an adequate pulmonary reserve has been stressed. Irreversible changes may exist in the lung even though myocardial function is adequate. Two patients in this series who were calculated poor risks died during postoperative hospitalization.

Although an early postoperative mortality of 6 per cent may be considered reasonable, this figure should be, and can be reduced. We believe that, with judicious consideration of the foregoing categories, mitral commissurotomy can be carried out under proper circumstances with an expected mortality rate of 2 to 3 per cent. A mortality rate of less than 2 per cent should be expected if only young patients with uncomplicated mitral stenosis were to be selected for surgery, but such a timorous policy would reflect little credit on the surgeon and do a grave injustice to many patients.

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Review Article:

QUINIDINE IN THE TREATMENT OF AURICULAR ARRHYTHMIAS

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Preface

THE clinical efficacy of a drug is determined by weighing the anticipated benefits from its use against the danger of toxic effects. Lack of appreciation of this fact has led to misunderstanding relative to the value of quinidine. When properly employed, quinidine is a safe and effective drug in the treatment of certain auricular arrhythmias. Increasing interest in the cardiac arrhythmias in recent years warrants a review of the toxic and therapeutic effects of quinidine.

Physiologic Action, Dosage, and Toxic Effects of Quinidine

Quinidine prolongs conduction recovery in the auricular muscle and slows the rate of discharge from ectopic foci. It raises the threshold in experimental production of auricular arrhythmias.[1] The importance of decrease in vagal tone secondary to the use of the drug is not known.

It has been demonstrated that the maximum level of concentration in the blood after oral administration of quinidine is attained in about two hours.[2] For this reason, when quinidine is used in the treatment of important auricular arrhythmias, it should be given at intervals of two hours, usually in a dosage of 0.4 Gm. of quinidine sulfate for five doses. Quinidine has cumulative action, so that gradually increasing concentrations in the blood are achieved. Even 12 hours after the last dose, the blood level remains about 40 per cent of the maximum level; for this reason, the same dosage schedule on the second day may be of therapeutic benefit. If the arrhythmia persists, the dosage may be increased to 0.6 Gm. every two or three hours for four or five doses, and subsequently a dosage of 0.8 to 1.0 Gm. or more every three hours for four doses may be tried if toxic manifestations have not occurred. The total daily dosage should not exceed 4 to 6 Gm. Quinidine may be given intramuscularly or intravenously, but indications are rare for parenteral therapy of auricular arrhythmias.

Fear of toxic reactions has limited the use of quinidine. Because it is an isomer of quinine, symptoms of cinchonism may occur. Nausea, vomiting, and diarrhea are common. Nausea and vomiting may necessitate discontinuance of therapy. Diarrhea may be controlled by symptomatic measures. Skin eruptions, purpura, and fever are rare and are indications for termination of treatment. Electrocardiographic changes and ventricular arrhythmias may result from

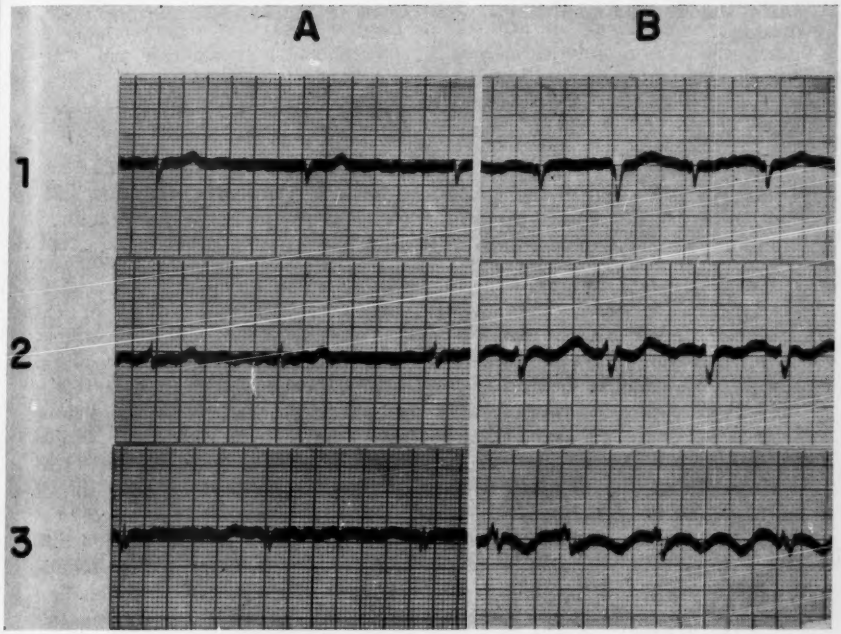

Fig. 1. (A) Control record prior to quinidine therapy for auricular fibrillation. (B) Record that shows slowing of the auricular rate, increase in the Q-T interval, and prolongation of intraventricular conduction due to the toxic effect of quinidine.

quinidine therapy. The earliest electrocardiographic effect is prolongation of the Q-T interval (fig. 1A), and this is not a contraindication to continued use of the drug. Auriculoventricular conduction disturbances may occur and if severe are an indication for termination of therapy. Prolongation of intraventricular conduction may result when large doses of quinidine are employed (fig. 1B). If the duration of the QRS complex exceeds the normal for the individual by more than 50 per cent, the drug should be discontinued. Ventricular premature contractions occur occasionally and may lead to the development of ventricular tachycardia. This serious arrhythmia is seen most frequently after the intravenous use of quinidine and probably accounts for the majority of the fatalities reported. It rarely develops if other electrocardiographic and clinical warnings of toxicity have been heeded. Cardiac arrest may occur but it is extremely rare. Daily electrocardiograms should be taken during treatment, and when large doses of quinidine are used, records should be made and interpreted before each successive dose of the drug is given. If electrocardiographic evidence of serious toxicity is seen, treatment should be terminated. Since hypotension is common during the administration of quinidine, the

patient should remain in bed each day during treatment and for several hours thereafter.

Treatment of Auricular Arrhythmias

Auricular premature contractions rarely require the use of quinidine and are often better controlled by other measures, such as reassurance, rest, and mild sedation. When disturbing symptoms accompany the premature contractions, quinidine may be helpful. Moderate dosages are required in most cases, and in some instances the irregularity may not be eliminated even though large dosage is employed.

Auricular paroxysmal tachycardia is a common arrhythmia, and most attacks are of brief duration. Prolonged episodes require some therapeutic measure. Carotid sinus pressure should be tried initially. Frequently neostigmine, 0.5 to 10 mg. subcutaneously, will terminate the attack, particularly if carotid sinus pressure is applied about 15 minutes after administration of the drug. If this treatment is not effective, digitalis intravenously, usually in the form of 0.8 mg. of lanatoside C, should be tried. In some instances, carotid sinus pressure is required after the patient has received digitalis, the maneuver being tried 15 to 30 minutes after completion of the intravenous injection. Quinidine is not a very potent drug in the treatment of auricular paroxysmal tachycardia. Occasionally it may be useful in the prevention of recurrent attacks. A dosage of 0.4 Gm. four times daily is employed in most instances.

Auricular paroxysmal tachycardia with auriculoventricular block is a relatively rare arrhythmia and is resistant to treatment. In some cases it may be due to digitalis intoxication and can be eliminated by the use of potassium salts orally administered.[3] Quinidine therapy may be effective in cases not caused by digitalis intoxication.

Auricular flutter is a serious arrhythmia that usually occurs in patients with organic heart disease. Quinidine is frequently employed in treatment, but the arrhythmia can be terminated more often and safely by adequate digitalization. Digitalis in a dosage of 0.1 Gm. three times daily for as long as three weeks may be required before the auricular mechanism is converted to auricular fibrillation. Cessation of digitalis therapy after development of auricular fibrillation will result in restoration of sinus rhythm in many instances. If auricular fibrillation persists, it can then be terminated by the use of quinidine. Occasionally it is necessary to use quinidine in the treatment of auricular flutter if symptoms of digitalis intoxication occur.

Auricular fibrillation is the most frequent important auricular arrhythmia. It may exist in patients who have organic heart disease or it may occur in the absence of other clinical evidence of cardiovascular disease. Auricular fibrillation is usually present in patients who have systemic emboli in the absence of acute myocardial infarction. Pulmonary emboli may also occur. The increased

risk of embolization in patients with auricular fibrillation constitutes one of the major reasons for restoration of sinus rhythm. Rarely, emboli may occur when auricular fibrillation has been converted to sinus rhythm, and for this reason it formerly was believed that a history of embolization constituted a contraindication to quinidine therapy. However, embolic complications are frequent in patients who have auricular fibrillation and in whom no attempt has been made to restore sinus rhythm. Sokolow[2] considers a history of previous emboli an indication for treatment. He found that in patients who had had previous embolic accidents, further embolization at the time of re-establishing sinus rhythm was less frequent than in patients who had experienced no previous embolic episodes. The cardiac output is reduced in persons who have auricular fibrillation associated with organic heart disease, and restoration of sinus rhythm usually results in an increased output.[4,5]

An attempt to restore normal sinus rhythm should be made in most cases of auricular fibrillation. Long-standing auricular fibrillation, a history of embolization, the presence of cardiac enlargement, a past history of congestive heart failure and mild conduction disturbances are not contraindications to treatment. In the presence of mitral stenosis it is more difficult to restore sinus rhythm, and auricular fibrillation is likely to recur even though prophylactic quinidine is employed. If the arrhythmia is not well tolerated and there is some contraindication to operative treatment of mitral stenosis, quinidine therapy may be tried. Angina pectoris may disappear after the development of auricular fibrillation, and if it does, restoration of sinus rhythm should not be attempted. Subacute bacterial endocarditis and severe conduction defects constitute contraindications to the use of the drug. Aged persons often tolerate auricular fibrillation well, and there seems to be a higher incidence of toxic effects from the use of the drug in the aged. In elderly patients, therefore, quinidine should not be employed if auricular fibrillation has not resulted in congestive heart failure or embolization. Quinidine is not effective in the treatment of auricular fibrillation due to thyrotoxicosis until after the thyroid disease has been controlled. Acute myocardial infarction may result in the development of auricular fibrillation. The ventricular rate should be reduced by the administration of digitalis. In many cases sinus rhythm will return spontaneously within a few days. Quinidine therapy may be used after recovery from the myocardial infarction if the arrhythmia persists.

Anticoagulants have been used prophylactically to decrease the risk of embolization on restoration of sinus rhythm. It is doubtful that such treatment is helpful, and it is not recommended. Congestive failure should be eliminated, if possible, before quinidine is employed. Lewis[6] emphasized the need for digitalis to control the ventricular rate before the administration of quinidine, and this remains an important principle. Quinidine slows the auricular rate and has a vagal blocking effect. These factors tend to increase the ventricular rate, sometimes to an alarming degree if 1:1 conduction is established. Therapeutic doses of digitalis do not decrease the effectiveness of quinidine and do not "fix" the heart in fibrillation.

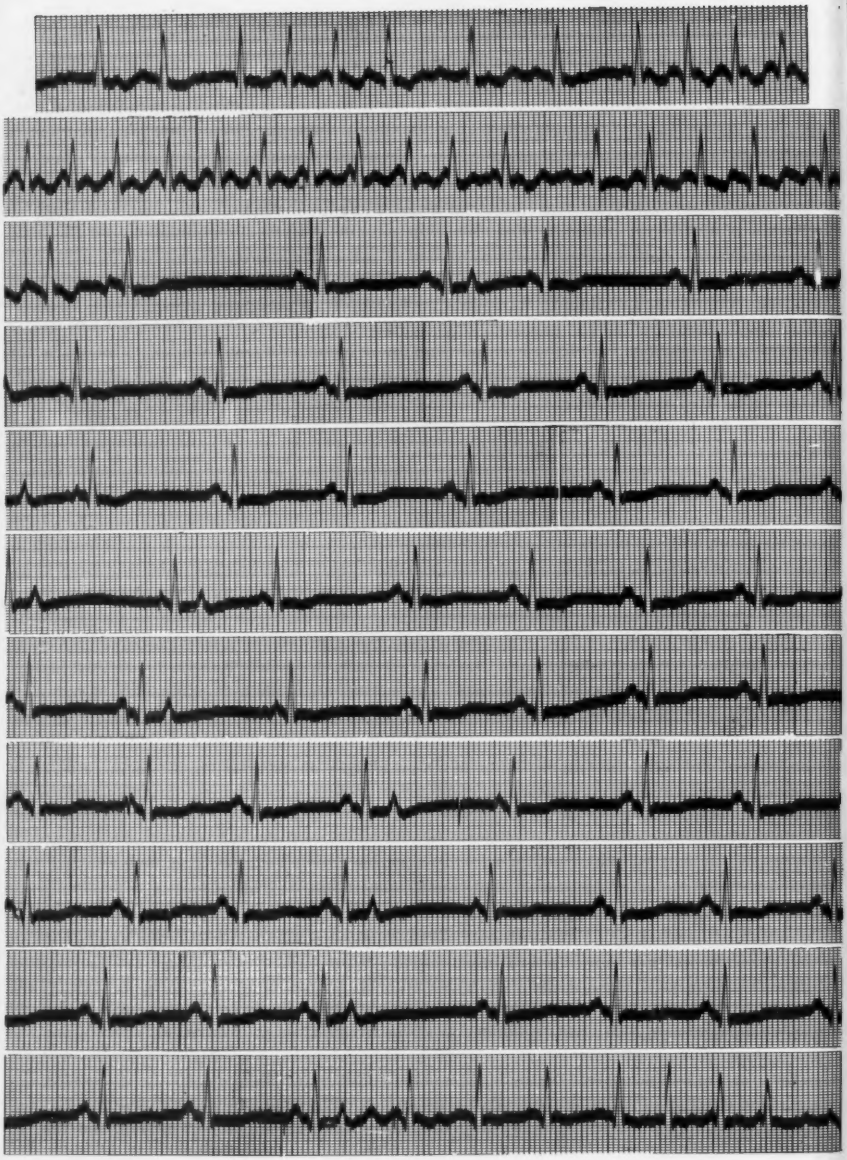

Fig. 2. Continuous strip of lead II that shows variable auricular mechanisms resulting from the therapeutic effect of quinidine.

The auricular rate decreases gradually during quinidine treatment of auricular fibrillation and may reach levels below 200 per minute before sinus rhythm is restored. The electrocardiographic appearance may resemble that of auricular flutter, but the auricular complexes are not perfectly regular. In some instances, typical auricular flutter may occur. By taking a continuous electrocardiogram it can be shown that restoration of sinus rhythm is not always a single, sharply defined phenomenon. Figure 2 shows a record of lead II taken during quinidine treatment of auricular fibrillation. The rhythm first returned to normal about two and one-half hours after the drug was first taken, but recurrent periods of auricular fibrillation or flutter of decreasing duration alternated with sinus rhythm until finally normal sinus rhythm had become established. Sinus rhythm may be restored during the night, five to ten hours after the last dose of quinidine. For this reason, the cardiac mechanism should be determined before quinidine is given each day.

In about 75 per cent of cases quinidine therapy for chronic auricular fibrillation is successful. After restoration of normal rhythm, prophylactic quinidine is employed to decrease the likelihood of reversion to auricular fibrillation. Usually 0.4 Gm. is given four times daily. If large amounts of drug have been required in treatment, prophylactic doses of 0.6 or even 0.8 Gm. may be required, but this is unusual. The drug should be administered for about one month, because auricular fibrillation is most likely to recur during the first few weeks after treatment. If the arrhythmia recurs after termination of prophylactic quinidine, restoration of sinus rhythm should be followed by permanent quinidine prophylaxis.

Paroxysmal auricular fibrillation is best treated by digitalization. The duration of the paroxysms is self-limited. Quinidine is often effective prophylactically. It is given in a dosage of 0.4 Gm. four times daily, though larger doses may be required occasionally.

SUMMARY

The use of quinidine in the treatment of auricular arrhythmias is reviewed. Beneficial results and toxic effects, methods of administration, and clinical indications are presented.

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Detailed programs of the following postgraduate courses that are scheduled for the fall will appear in the July issue of the QUARTERLY.

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(Tentative dates)

OSTEOID OSTEOMA

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and

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OSTEOID osteoma is a most interesting and unusual lesion of bone. Although relatively uncommon, this lesion must always be considered as a possible cause of pain in the extremities or in the backs of patients between the ages of 10 and 30 years. The disease occurs most frequently in the second decade of life and is encountered twice as often in males as in females. Since the clinical signs and the clinical course of an osteoid osteoma are unique, being unlike those of any other lesion of bone, a diagnosis of the condition can often be made even without histologic verification.

Osteoid osteoma was first described as a clinical entity by Jaffe[1] in 1935. However, five years earlier in 1930, Bergstrand[2] published a detailed summary of two cases of a rare benign osteoblastic lesion—one in a metatarsal and one in the phalanx of a finger. Preoperatively, Bergstrand had believed that these lesions were osteogenic sarcomas, but, after examining the involved areas of the resected bones, he concluded that the lesions were neither inflammatory nor neoplastic but probably were due to embryonal rests. These two cases of Bergstrand's were osteoid osteomas, but Jaffe receives the credit for initially describing the clinical and pathologic features of this most unusual lesion.

Jaffe applied the term "osteoid osteoma" to this lesion of bone because he believed it to be a true, benign, osteoblastic tumor consisting of osteoid and atypical bone. The exact nature of osteoid osteomas is still a matter of debate among pathologists, radiologists, and orthopedists. Brailsford,[3] MacKenzie,[4] and Hellner[5] believe that these lesions represent only a low-grade, cortical or subcortical, nonsuppurative inflammation in bone. The absence of any clinical signs of infection, together with the absence of any bacteriologic or microscopic evidence of inflammation in surgical specimens, has led most investigators to the conclusion that osteoid osteoma should be classified as a tumor of bone.

However, if this condition is a true neoplasm of bone, it is unlike any other benign tumor of bone. The extensive sclerosis of bone which is so often associated with an osteoid osteoma, is not seen with any other benign tumor of bone. The apparently spontaneous healing of the lesion makes it seem unlikely that this condition could represent a true tumor of bone. Only a very few cases of osteoid osteoma have been reported in patients more than 40 years of age. Sherman[6] and Moberg[7] have reported a few cases with clinical and roentgenographic findings typical of osteoid osteoma, in which the disease healed over a period

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of years, and the clinical symptoms disappeared with cessation of the progressive development of the nidus or circumscribed core of the lesion. In these cases, the roentgenographic changes persisted for many years, but gradually diminished. None of these cases, of course, was histologically verified, since biopsy would alter the natural course of the disease.

Trauma is believed to play only a small role or none in the production of an osteoid osteoma. In only a few of the reported cases does there seem to be any definite relationship between an injury and the development of the lesion. Furthermore, the majority of these lesions are located in portions of the skeleton not readily exposed to trauma.

Other authors have suggested that an osteoid osteoma may be the result of an embryonic rest, a healing infarct of bone, or a healing giant-cell tumor. Careful histologic studies have failed to substantiate any of these etiologic possibilities.

DIAGNOSIS

No matter what the exact nature or origin of an osteoid osteoma may be, this condition is certainly a definite clinical entity. Pain is the most important symptom of the condition. The pain is usually fleeting at the onset but gradually becomes more constant and more severe. The pain may be aggravated by exercise and is very commonly worse at night. A child with an osteoid osteoma will often be awakened from a sound sleep at night by a severe aching pain in or near the region of the lesion. In lesions about the hip, the pain may be referred to the knee; but, as a rule, the pain of an osteoid osteoma is localized directly over the site of the lesion. Small doses of aspirin almost always give prompt temporary relief from the pain. Pain may antedate, by several weeks, any other clinical or roentgenographic evidence of the disease.

On physical examination there is usually acute tenderness immediately over the site of the lesion. Some swelling may be present, caused either by actual thickening of the bone or by associated edema of the soft tissues adjacent to the lesion. However, there are no other evidences of inflammation, such as local redness, increased warmth, or local adenopathy; and there are no systemic evidences of infection, such as elevated temperature or leukocytosis. A limp may be present when there is a lesion involving one of the bones in a lower extremity; in fact, occasionally a limp may be noticed before pain has become the primary complaint. When the osteoid osteoma lies in close proximity to a joint, there may be associated inflammatory changes within the joint. These changes subside spontaneously after removal of the lesion. When the disease involves the cervical spine, a torticollis may be present; when the dorsal or lumbar spine is involved, a scoliosis may result.

Roentgenographic findings are to some degree dependent upon the age and the location of the lesion. The typical roentgenogram reveals an oval-to-round area of decreased density surrounded by an area of sclerotic bone. This inner area, or so-called "nidus," usually measures from 0.5 to 2.5 cm. in diameter. The nidus may be obscured by the overlying sclerotic bone, and overexposed films taken at different angles may be necessary before the lesion can be seen.

The regional sclerosis or hypertrophy of bone is greatest when the nidus is located near the cortex of a tubular bone; there is much less reaction if the lesion is more superficially located or if it occurs in cancellous bone. The nidus itself may appear uniformly translucent or may be mottled with irregular, sclerotic spicules of bone. Moberg[8] has recently reported a case of osteoid osteoma of the fourth metatarsal in which reactive formation of bone was not restricted to the bone in which the nidus was situated but was also present on two adjacent bones—the third metatarsal and the proximal phalanx of the fourth toe. The periosteal thickening was noted only on the lateral side of the third metatarsal, that is, on the side of the bone immediately adjacent to the metatarsal containing the osteoid osteoma.

Osteoid osteoma apparently is always a single lesion. There may be a recurrence of the lesion after incomplete removal of the nidus, but there is no evidence that more than one such lesion occurs in any one person.

Grossly, the central nidus is usually reddish in color and sharply demarcated from the surrounding bone. In more mature lesions, the color becomes less red and the cut surface shows reddish-brown flecks mixed with a pearl-gray matrix; the flecks represent calcified osteoid. The nidus may be soft and friable in the early stages, or firm and gritty as the tumor matures. When the lesion is within or near the cortex, the periosteum is thickened and edematous. There is no evidence that the lesion ever has invaded or broken through the periosteum or ever has metastasized.

The histologic appearance of an osteoid osteoma is characteristic: the nidus presents a stroma of vascular, richly cellular, immature, connective tissue containing all the elements necessary to the development of membranous bone, from primitive connective-tissue cells to osteoblasts. Interspersed throughout the stroma are islands and trabeculae of osteoid, mature or immature, depending upon the stage of development of the lesion. In some areas, this osteoid may be partially calcified. No inflammatory cells are seen and there are no signs of vascular necrosis or of old hemorrhage. About the osteoid are arranged large numbers of osteoblasts and a few osteoclasts. As the periphery is approached, the osteoid is more uniformly calcified. It is the osteoid tissue of the nidus itself which is characteristic; the peripheral heavy trabeculae represent normal sclerotic bone.

REPORT OF CASES

Since 1940, 17 cases of osteoid osteoma have been seen here. Eleven of these patients were males, and six were females. The youngest patient was six years of age, and the oldest was 40. Eleven patients, or 65 per cent, were less than 30 years of age.

In this group the distribution of the lesions according to their locations was typical of that in other reported series. The table lists the sites of these 17 lesions; 75 per cent of this group of osteoid osteomas was located either in the femur or in the tibia.

TABLE

Sites of Osteoid Osteoma in 17 Cases

Location	No. of Cases
Neck of femur	3
Shaft of femur	5
Tibia	5
Pubis	2
Carpus	1
Metacarpus	1

Four cases from this group are described here to illustrate the clinical features of osteoid osteoma and to emphasize certain aspects of the treatment of this condition.

Case 1. A 33 year old housewife was first seen on September 22, 1948. She stated that two years previously she had noticed the gradual onset of pain in the right hip with some radiation down the lateral aspect of the thigh. The pain had gradually increased in severity since its onset, and at the time of initial examination the pain was fairly constant but was always worse at night. A single aspirin tablet would give temporary relief from the pain. It was not aggravated by activity and was not relieved by rest. There was no history of any antecedent illness or injury. In January 1948 an exploratory operation had been performed to determine whether there was any evidence of inflammation in the lateral femoral cutaneous nerve. The patient was told by her surgeon that this nerve was not severed because no inflammation was found about it.

Physical examination revealed that the patient walked with a limp on the right leg. Internal rotation of the right hip was restricted to 15 degrees; other motions of the hip were normal. There was some deep tenderness over the anterior aspect of the right hip joint. The remainder of the findings of the general physical examination was essentially normal.

Laboratory studies, including urinalysis, blood count, hemoglobin determination, blood sugar content, Wassermann and Kahn tests, were all within normal limits. Roentgenograms of the pelvis and right hip, which the patient had had taken two months previously, showed no evidence of any bony abnormality except for slight cortical thickening along the inferior aspect of the femur with a small, oval, radiolucent area within this zone of sclerotic bone (fig. 1).

On November 2, 1948, the right hip joint was exposed through an anterior iliofemoral incision. The synovial lining of the hip joint was thickened, and there was an increased amount of fluid within the joint. On the anterior inferior aspect of the femoral neck was an area of roughened cortex. A marker was placed at this site and a roentgenogram was made which showed that this area coincided with the site of the nidus. A block of bone was then removed, measuring 15 by 10 by 6 mm., which included a small area of soft, reddish tissue corresponding in size with the small area of radiolucency seen on the roentgenogram. The walls of the cavity were then curetted, and another roentgenogram was made to be sure that the entire nidus had been removed.

Pathologic examination of the specimen revealed the typical histologic pattern of an osteoid osteoma. There was a well-defined layer of dense trabecular bone surrounding a small area in which the normal bony architecture was completely lost. This area was formed by thin, irregular, interlacing trabeculae of osteoid tissue, separated by relatively abundant, highly vascular, fibrous tissue containing osteoblasts and numerous multi-

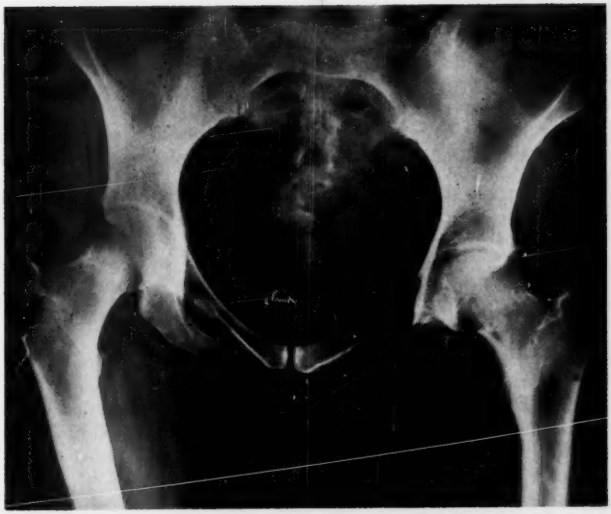

Fig. 1. (Case 1) Preoperative roentgenogram of pelvis. On the right there is a small radiolucent area along the inferior aspect of the femoral neck with some sclerosis of bone extending down to the lesser trochanter.

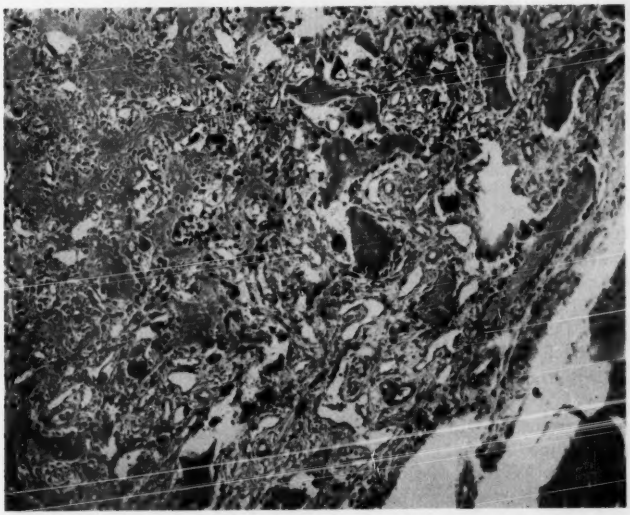

Fig. 2. (Case 1) Photomicrograph (X 90) of a portion of the osteoid osteoma removed from patient. Numerous small trabeculae of osteoid tissue are separated by a loose vascular connective-tissue stroma containing osteoblasts and osteoclasts.

nucleated giant cells of the osteoclastic type (fig. 2). A biopsy of the synovial lining showed evidence of a nonspecific type of inflammation, characterized by small foci of hemorrhage and diffuse infiltration of the synovial membrane by lymphocytes and plasma cells.

On the first day postoperatively, the patient was certain that she no longer had the pain in the hip which she had had prior to the operation. She has remained well, with no symptoms referable to the right hip for the five and one-half years since the operation.

Case 2. A 38 year old shoe-salesman was first seen on May 19, 1948, with the complaint of constantly aching pain in his right wrist of about 15 months' duration. There was no history of any injury to the wrist, although the patient believed the condition might have been aggravated by playing tennis. Previous treatment had consisted of roentgenologic therapy, physical therapy, splints and casts, and had not produced even temporary relief of pain. Injections of procaine into the tender area, and aspirin gave temporary relief.

Examination revealed an area of marked tenderness over the dorsal aspect of the second carpometacarpal joint. There was slight restriction of motion in the right wrist but no swelling in the joint. Findings of a general physical examination were essentially normal, and routine laboratory studies, including urinalysis, blood count, blood sugar content and blood serology, were within normal limits. Roentgenograms of the wrist and hand failed to reveal any abnormality.

On September 10, 1948, approximately four months after initial examination, the tender area was surgically explored under local anesthesia. On the dorsal proximal aspect of the lesser multangular bone there was found a small osseous defect, approximately 0.5 cm. in diameter, which was filled with a strawberry-colored, gritty, fibrous tissue. This tissue was removed with a curet and sent to the pathology department for examination; histologic diagnosis of osteoid osteoma was made.

The patient was relieved promptly of the pain in the wrist and has remained well for almost six years after operation.

Case 3. A nine year old boy was first seen on December 7, 1951, with the complaint of pain in the right knee. The pain had been present intermittently for 18 months prior to examination and had first occurred when the patient had injured the knee while playing football. The pain would persist for several weeks at a time, and then would disappear almost entirely for several months. The boy would be awakened at night by pain in the knee which could be relieved by local heat and massage. The boy's parents noticed recently that he limped slightly on the right leg.

Physical examination revealed a well-developed, well-nourished boy, who walked with a slight limp on the right leg. There were 2.5 cm. of atrophy of the right thigh and 1.5 cm. of atrophy of the right calf, as compared with the left. There was tenderness over the medial femoral condyle. The right knee lacked the few degrees of hyperextension present in the left knee; otherwise, motion in the right knee was complete. There was no swelling within the joint. There was slight soft-tissue swelling over the medial femoral condyle.

Roentgenograms of the right knee showed a radiolucent area measuring 1 cm. in diameter in the medial condyle of the femur, midway between the epiphysial line and the joint cartilage. Within this radiolucent area the normal bony architecture had been destroyed and some irregular sclerotic bone was present (fig. 3).

Surgical treatment was postponed because the lesion was located within the femoral epiphysis and because, at the time of the initial examination, the patient's symptoms were not severe. The symptoms increased in severity during the next year, yet roentgeno-

grams taken every three or four months failed to reveal any change in the appearance of the lesion in the medial femoral condyle.

At operation on December 4, 1952, approximately one year after initial examination, the anterolateral aspect of the medial femoral condyle was exposed; a small window was made in the bone, and through this window the nidus was removed with a curet. Roentgenograms taken at the time of the operation showed that the entire lesion had been removed. Pathologic examination of the removed tissue disclosed a typical osteoid osteoma.

Two days postoperatively the child stated he no longer had any pain in the knee, and he has remained symptom free for one and a half years after operation. A roentgenogram of the knee in July 1953, seven months after operation, showed that the surgical defect in the medial femoral condyle had become completely filled in with normal cancellous bone.

Case 4. An 11 year old boy was first seen in the neurosurgical section on May 12, 1950. He had been referred to that department by his local physician because of a suspected neurologic condition producing pain in the child's left groin and hip. This pain had begun insidiously in June 1949, about one month following an uncomplicated

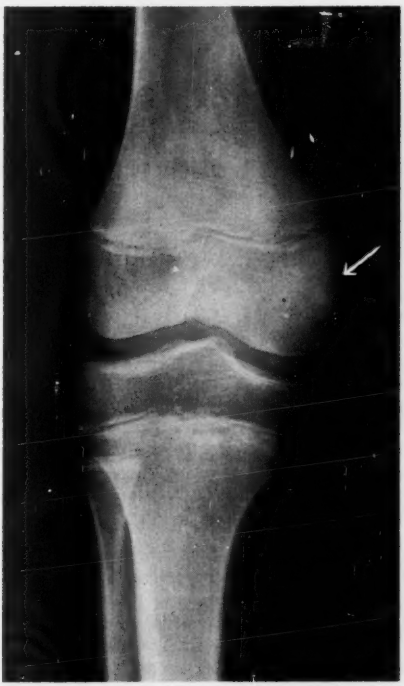

Fig. 3. (Case 3) Preoperative roentgenogram of knee, showing osteoid osteoma as a radiolucent area in medial condyle of femur, midway between the epiphysial line and the joint cartilage. The lesion being located in cancellous bone, there is very little surrounding sclerosis of bone. The arrow points to the lesion.

appendectomy. There was no history of any injury. The pain was described as "a toothache in the hip." The pain was aggravated by excessive exercise and relieved to some extent by rest and aspirin. At first the pain had been present only at night, awakening the child from a sound sleep. During the few months prior to examination, the pain had been present also during the day. The child was observed to limp on the left leg when the pain was present. He had been hospitalized elsewhere for two months because of a tentative diagnosis of tuberculosis of the hip, but at the time of his discharge the physician told the boy's parents that no disease had been found.

Results of the physical examination were essentially negative, except for definite tenderness to deep pressure in the left groin and 1 cm. of atrophy of the left thigh as compared with the right. There was no restriction of movement in the left hip joint.

Roentgenograms of the hip showed a somewhat ill-defined radiolucent area in the superior ramus of the left pubis. There was a shallow zone of sclerotic bone about this area (fig. 4).

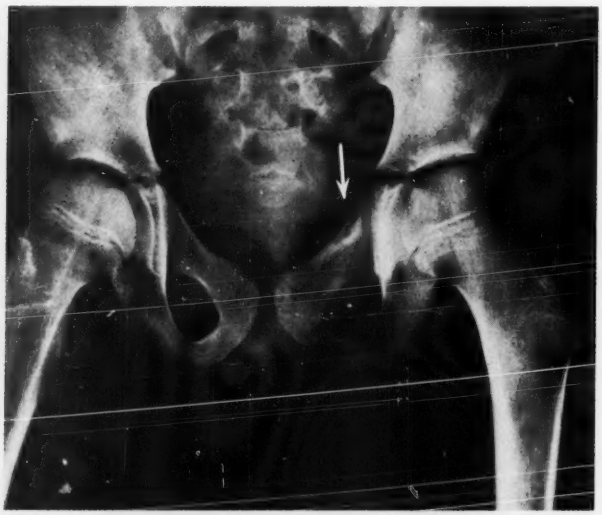

Fig. 4. (Case 4) Preoperative roentgenogram of hip. The arrow points to an irregular area of decreased density in the superior ramus of the pubis near the acetabulum. The nidus is not sharply defined and is surrounded by a narrow zone of dense sclerotic bone.

Operation was performed on June 8, 1950, approximately one month after initial examination; the superior ramus of the left pubis was exposed subperiosteally. Roentgenographic examination accurately localized the diseased area of the bone, which was then excised piecemeal with osteotome and rongeur. Many small pieces of bone were sent to the pathology laboratory for examination. Microscopic examination showed that the surgical specimen had the characteristic appearance of an osteoid osteoma. Another roentgenogram of the surgical area, in the operating room, revealed that the entire radiolucent area had been removed.

The child was relieved of his pain by the second postoperative day. Four years after the operation there had been no recurrence of any discomfort in or about the left hip.

DISCUSSION

Once a physician has seen a patient with osteoid osteoma, he will always remember to consider this lesion as a possible cause of pain in the bones of a child or young adult. The dramatic and permanent relief from pain which is obtained by surgical removal of the nidus will leave little doubt in the clinician's mind that this condition represents a real pathologic and clinical entity. Although it has been observed that osteoid osteomas will eventually heal spontaneously over a period of several years, surgical excision of the lesion is the treatment of choice. The risk of the operation is slight when compared with the years of continued suffering that the patient will have to endure if the nidus is not removed.

All of the patients in our series were successfully treated by surgical removal of the lesions. Two of the patients operated upon here and one of the patients operated upon elsewhere, each required two operations to remove the nidus completely. The entire nidus must be removed or the patient will continue to have pain. We have learned that roentgenographic control is imperative in the operating room: to locate the lesion and, before the incision is closed, to ascertain whether the nidus has been completely removed.

Occasionally, as in case 2, the nidus at the time of operation will be recognized as a well-encapsulated, reddish mass of fibrous tissue. In most of our cases, however, the central lesion has not been well defined, and only by studying roentgenograms made at the time of the operation could we be certain that the lesion had been completely removed. In order to cure osteoid osteoma, it is necessary to remove only the nidus—not the adjoining sclerotic bone. A block dissection of the nidus may be performed, provided that this does not entail removal of too great an amount of bone. A few cases[9] have been reported of fracture and of nonunion following too radical excision of an osteoid osteoma. The majority of our cases were not treated by block excision.

Pathologic verification of the nature of the lesion was not obtained in seven of our cases. In three of these, the surgical specimen was sent to the bacteriology laboratory for culture in the belief that the condition represented an inflammatory lesion of bone. But these cultures, as well as cultures taken from most of the other cases, were negative. In four cases the pathologist was unable to demonstrate the typical microscopic picture of an osteoid osteoma in the fragments of bone removed at the time of the operation. In these seven cases without pathologic confirmation of the diagnosis, the clinical course and the roentgenograms were so characteristic of osteoid osteoma that we believe we are justified in including them in this series.

Sherman[10] has pointed out that osteoid osteoma may be associated with changes in the adjacent joint. In case 1 of our report there was noted marked thickening of the synovial lining of the hip joint, as well as considerable increase in the amount of fluid within the joint. Microscopic examination of the synovial lining, however, failed to reveal any evidence of active inflammation. In case 3 there were also some arthritic symptoms noted in the knee joint, although the

joint itself at the time of operation showed no evidence of arthritic changes. Case 2 also presented some arthritic symptoms, referable to the wrist joint.

In case 3 the osteoid osteoma was located within the distal femoral epiphysis. The presence of an osteoid osteoma within an epiphysis is most unusual.

SUMMARY

Although the etiology and exact nature of osteoid osteoma have not yet been determined, the roentgenographic and physical findings in patients with this unusual lesion of bone are so typical that this condition must be accepted as a clinical entity.

The findings in a series of 17 cases of osteoid osteoma seen here since 1940 are presented. Four of these cases are described in detail to illustrate the clinical course of the disease.

Complete surgical removal of only the nidus, or central core of the lesion, is all that is necessary to obtain an immediate permanent cure.

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THE USE OF RADIOACTIVE PHOSPHORUS* IN THE DETECTION OF INTRAOCULAR TUMORS

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INTRAOCULAR tumors often present a difficult diagnostic problem that involves the important decision of whether or not to enucleate an eye. When the eye that is suspect is the better of the two, the decision is critical. Radioactive phosphorus (P^{32}) was used as a diagnostic aid in 24 cases of intraocular lesions. The purpose of this report is to present the findings in this group.

Radioactive phosphorus was used by Low-Beer[1] in 1946, in the detection of tumors of the breast. In 1949, Selverstone, Solomon and Sweet[2] reported its value in the location of tumors of the brain. As concerns the eye, in 1951 Dunphy and Selberstone[3] showed that P^{32} concentrated in the vascular more than in the nonvascular tissues and intraocular fluids.

The use of P^{32} intravenously in the detection of intraocular tumors was first reported by Thomas, Krohmer and Storaasli,[4] who published findings in eight cases in 1952. Others have since reported their experiences.[5-7]

TECHNIC

P^{32} is used because it emits a beta radiation that easily can be detected with a Geiger counter. The average range of these beta rays in penetration of tissue is 2 mm., although the most penetrating may travel as deep as 6 mm. The half-life of the isotope is 14.3 days.

Eyes were anesthetized with 0.5 per cent tetracaine (pontocaine) hydrochloride. Five-hundred microcuries (0.5 millicuries) of sterile P^{32} (in saline solution) was then injected intravenously and counts were started immediately over the suspected area, and a corresponding area in the unaffected eye. An end-window Geiger tube of 6-mm. diameter was used and held directly against the sclera (fig. 1). One must be careful not to hold the Geiger tube over a rectus muscle, as this will have the undesirable effect of artificially increasing the count. Haigh and Reiss[8] have shown that intravenous P^{32} shows its greatest concentration in the uveal tract and rectus muscles soon after injection, and then levels

* *The radioactive phosphorus used was supplied by Abbott Laboratories on authorization from the Isotopes Division, U. S. Atomic Energy Commission.*

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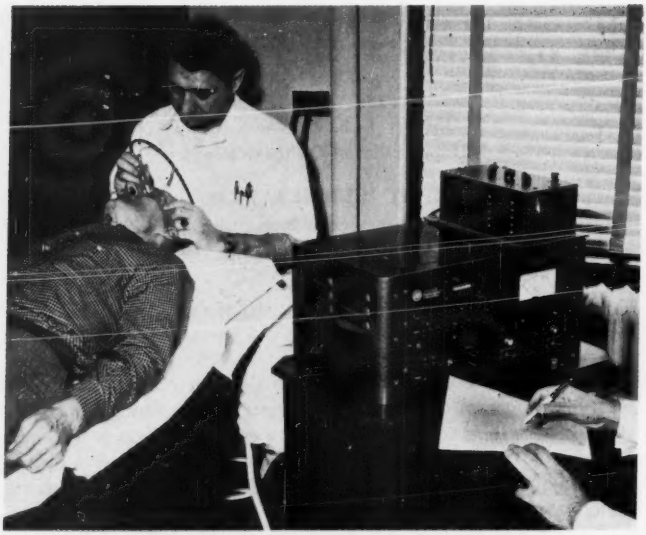

Fig. 1. The Geiger tube is being applied to the sclera.

off and finally gradually falls in concentration as the tracer is removed from the blood. Localization of the suspected lesion by ophthalmoscopic examination is important before starting the test, so that the counter can be applied as nearly as possible over the lesion site.

Counts on the Geiger scaler were taken for one hour at one-minute intervals. In some cases counts over both eyes were also taken after 24 hours, since the diagnosis of neoplasm is definitely indicated if the higher uptake in the affected eye is maintained for 24 hours.

The concentration of P^{32} in tumor tissue is illustrated by a radioautograph

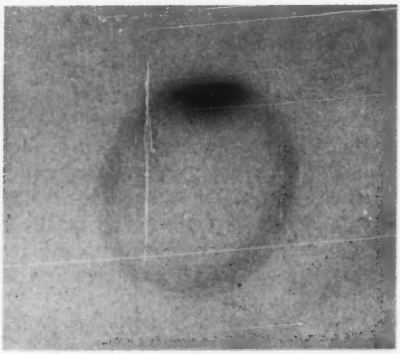

Fig. 2. Radioautograph illustrating the concentration of P^{32} in tumor tissue.

(fig. 2). Just what factors produce the increased count in a tumor are not known. One seems to be increased metabolic activity (phosphate turnover) of the nucleoproteins of the tumor; another may be vascularity of the tumor. Bettman and Fellows[6] have shown that vascularity is one important factor; they reported a higher count in a portion of a melanoma that was extremely vascular as compared with that in a much less vascular part of the same tumor.

RESULTS

A total of 24 cases was studied. The clinical diagnosis and the positive or negative character of the selective uptake ratio for each case are listed in the

TABLE
Findings with Intravenous P^{32} in 24 Cases of Intraocular Lesions

Clinical Diagnosis	No. of Cases	Character of Selective Uptake Ratio (P^{32} Isotope)	
		Initial	24 hr.
Melanosarcoma	7	+	+
	3	—	—
Metastatic carcinoma	1	+	Not done
Retinoblastoma	1	+	+
Melanoma iris	1	—	—
Thinning of sclera with ciliary body showing through	1	—	Not done
Retinal detachment	4	—	—
Retinal detachment with massive hemorrhage	1	+	Not done
Intraocular hemorrhage	1	—	—
Choroiditis	3	—	Not done
Macular cyst	1	—	—
	Total 24		

table. The selective uptake ratio was recorded as the ratio of the count in the affected eye to that over a corresponding area in the unaffected eye. Roughly two thirds (seven of ten) of the melanosarcomas initially had a positive P^{32} uptake ratio that remained high at the end of 24 hours. Three cases of melanosarcoma had low uptake ratios that were considered not diagnostic. The lesions

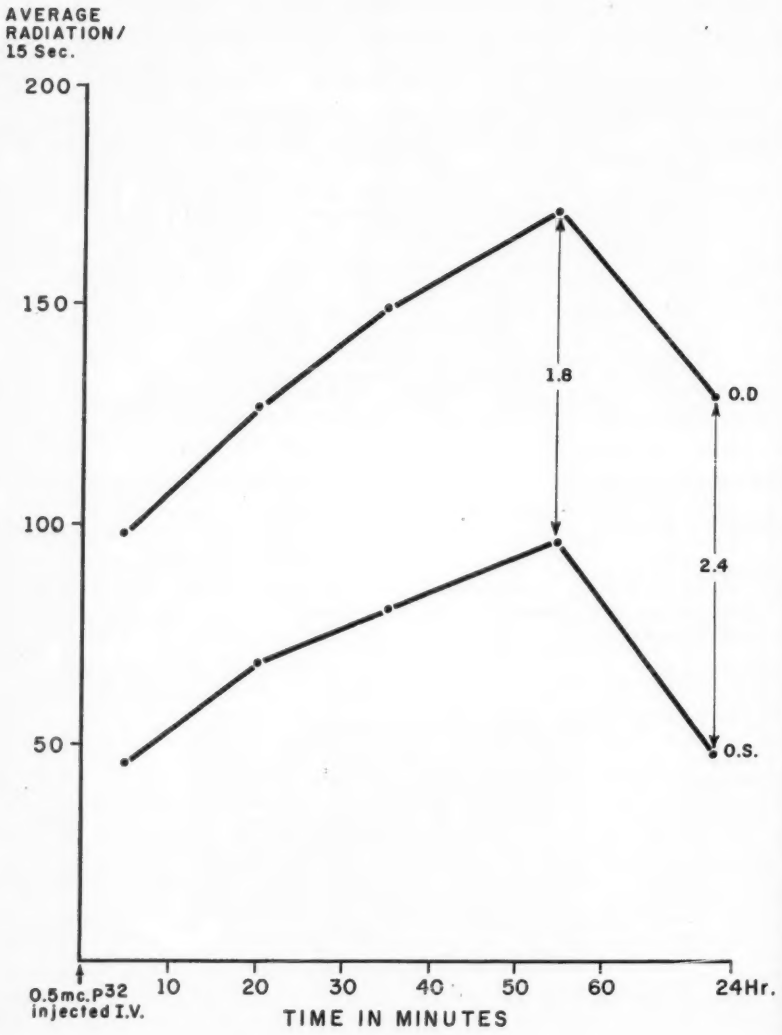
MELANOSARCOMA, CILIARY BODY O.D.
AVERAGE RADIATION/ 15 Sec.
200
150
100
50
1.8
2.4
O.D
O.S.
0.5mc.P32 injected I.V.
10
20
30
40
50
60
24Hr.
TIME IN MINUTES

Fig. 3

in these three cases were small and posteriorly situated. One retinoblastoma had a strongly positive uptake ratio initially and at the end of 24 hours. One metastatic carcinoma initially had a strongly positive uptake ratio. One falsely positive initial result was recorded from a retinal detachment with massive hemorrhage. Observations were not done at 24 hours in these two cases. The 11 remaining were cases of non-neoplastic lesions showing no abnormal distribution of P^{32}.

Krohmer and his associates[7] state from their figures on anterior segment lesions that a selective uptake ratio of 1.4 or higher is very suggestive of tumor, while a selective uptake ratio of less than 1.2 is good evidence of a non-neoplastic

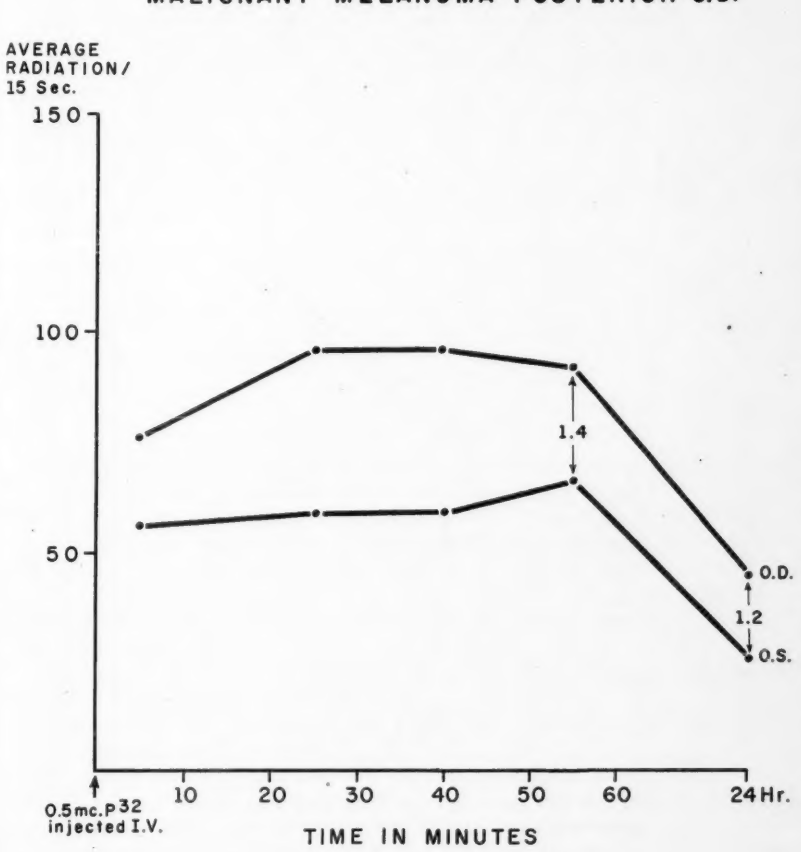

Fig. 4

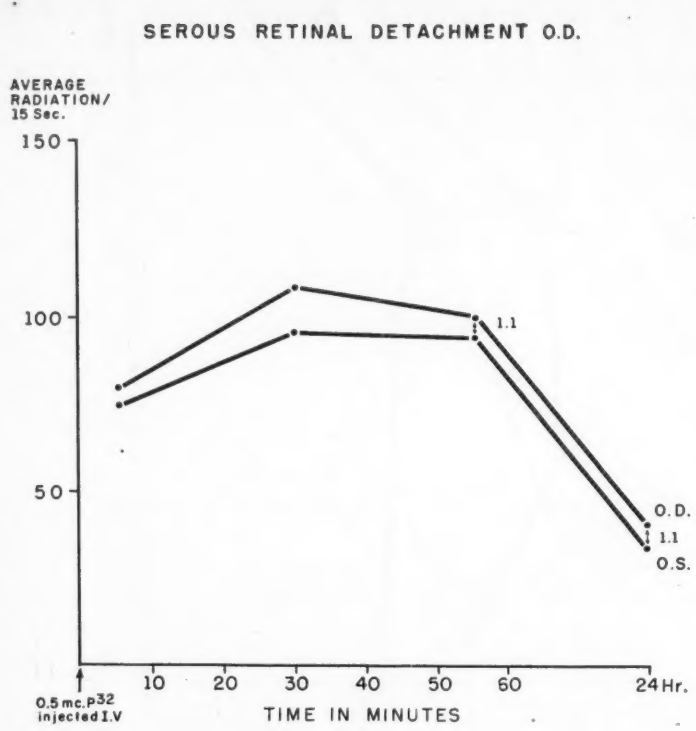
SEROUS RETINAL DETACHMENT O.D.
AVERAGE RADIATION/ 15 Sec.
150
100
50
1.1
O.D.
1.1
O.S.
10
20
30
40
50
60
24 Hr.
0.5 mc. P32 injected I.V.
TIME IN MINUTES

Fig. 5

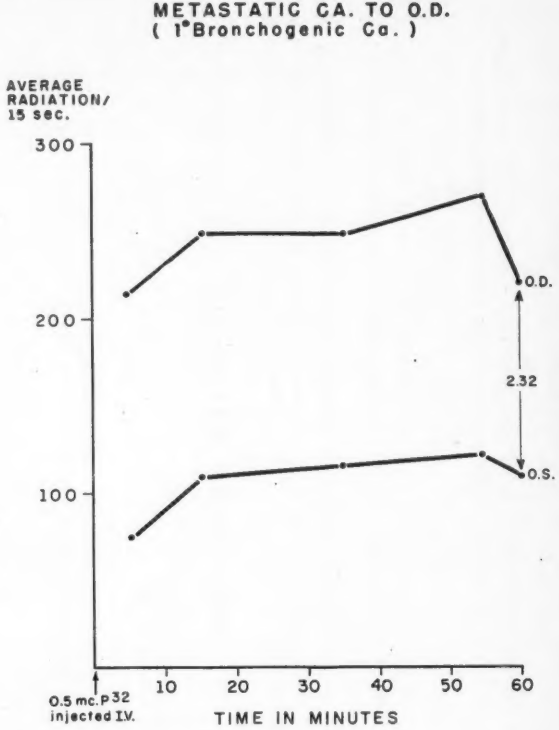
METASTATIC CA. TO O.D.
(1° Bronchogenic Ca.)
AVERAGE RADIATION/ 15 sec.
300
200
100
O.D.
2.32
O.S.
10
20
30
40
50
60
0.5 mc. P32 injected I.V.
TIME IN MINUTES

Fig. 6

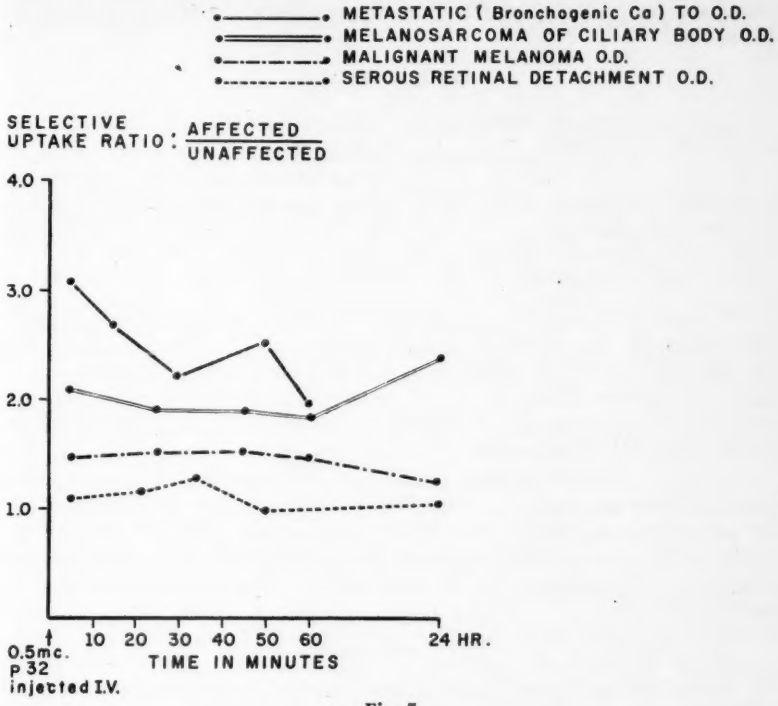

Fig. 7

process. When a tumor is located posteriorly, it is relatively inaccessible and it is difficult to place the counter in close apposition to it, so that selective uptake ratios are elevated over the eye, but only moderately so. This is demonstrated by comparison of figures 3 and 4. Figure 3 illustrates the uptake ratios of a melanosarcoma of the ciliary body which had an initial selective P^{32} uptake ratio of 1.3 rising to 2.4 at 24 hours. Figure 4 shows the uptake ratios of a posterior malignant melanoma. Here, the initial selective uptake ratio was 1.4 and at 24 hours 1.2.

Figure 5 shows nearly equal uptakes in the affected and unaffected eyes of a patient having retinal detachment.

Figure 6 shows a strongly positive P^{32} uptake of radiation by a metastatic lesion of bronchogenic carcinoma.

Figure 7 is a composite chart that illustrates the selective uptake ratios of four lesions. The ratio of 2.4 at the end of 24 hours of the anterior segment melanoma is clear evidence of a neoplastic process. The ratio of 1.2 of the posterior segment melanoma is a moderate elevation, and the ratio of 1.1 of the non-neoplastic lesion (retinal detachment) is not significant. The metastatic

carcinoma had a higher selective uptake ratio than that of a primary tumor of the eye.

APPLICATIONS

In all suspected cases of intraocular neoplasm, and in certain cases of retinal detachment, especially when a tear is lacking, this test is indicated.

Intravenous P^{32} may be of diagnostic aid in one-eyed persons if the lesion is so placed that counts can be made over comparable affected and unaffected areas in the same eye.

SUMMARY

Twenty-four intraocular lesions were examined by Geiger counter after intravenous injection of P^{32}. Non-neoplastic lesions (11) caused no inequality in localization of P^{32}. A significant increase in uptake of P^{32} was observed over nine lesions in eyes affected by malignant neoplasms. No significant increase was detected in three cases of melanosarcoma, apparently because the site of the tumor could not be approached with the counter.

It would appear from these results that P^{32} is a useful diagnostic aid in intraocular tumors, especially when the lesions involve the anterior half of the eye where a positive finding with P^{32} is of utmost importance. However, if the lesion involves the posterior half of the eye, a negative result does not rule out the presence of tumor, and for diagnosis one must still rely upon clinical findings and observations.

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MANAGEMENT OF CONTINUOUS SPINAL ANESTHESIA FOR GERIATRIC SURGERY

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SURGERY is considered in aged patients only when pathologic conditions supervene upon the involutionary changes that normally result from advancing years. Aged patients are classified as poor surgical risks because aging narrows the limits of physiologic response and increases the danger of surgery and anesthesia.

In selecting anesthesia for the aged patient, the status of his respiratory and circulatory systems must be carefully evaluated. The heart may be unable to withstand unusual stress, as simple atrophy of the heart and degenerative changes of the coronary vessels often are present.[1] Arteriosclerotic changes in the coronary and cerebral vessels form the groundwork for potentially catastrophic events should the blood pressure be allowed to fall precipitously and should it remain at hypotensive levels for any considerable time.* Hypotension is predisposed to by loss of elasticity of the peripheral vessels which impairs the rapid compensatory vasoconstrictor response to blood loss.

Spinal anesthesia by the continuous catheter technic provides safe anesthesia for operations in the abdomen, pelvis, and lower extremities of patients who are poor surgical risks. The indwelling catheter permits small and repeated injections of the anesthetic agents, thereby permitting the dosage to be adjusted specifically to each patient. With a segmental type of anesthesia[2] using minimal amounts of anesthetic agent, the surgeon operates under ideal surgical conditions, and little if any hypotensive effect of the anesthetic is noted. The patient is awake and cooperative; therefore, the protective reflexes are not disturbed. The small doses of anesthetic agent injected make it possible to terminate the anesthesia within a brief period simply by withholding further administrations. Severe hypotension, which rarely occurs, is treated with appropriate vasoconstrictor drugs. Continuous spinal anesthesia is therefore an appropriate technic for the poor-risk aged patient.

Physiology

Injection of 1 cc. of a 1 per cent (10 mg.) procaine solution within the intrathecal space is followed by blocking of all the components of the nerve roots, including sympathetic, somatic and motor, in the immediate vicinity of the tip of the catheter. The concentration decreases as the procaine diffuses up and down the spinal canal. Sensory and sympathetic blocks extend three to four segments, and motor paralysis extends two or three segments in either direction. The sympathetic nerve root block is negated somewhat by the fact

* *A fall in mean pressure greater than 25 per cent should not go uncorrected.*

that each ganglion inosculates via the sympathetic chain with two or three ganglia cephalad. Consequently, little if any hypotension is effected in this segmental type of continuous spinal anesthesia, and ideal safe operating conditions are presented.

Premedication

Premedications for the aged and poor-risk surgical patients are individually prescribed through consideration of each patient's general condition, temperament, age, and weight. Any deficiencies in premedication can be easily corrected in the operating room by the anesthesiologist. In most cases, morphine and atropine are suitable drugs. Demerol is preferred by some anesthesiologists who consider that it has less tendency to suppress respirations than does morphine. Actually, the depressant respiratory qualities of both drugs are about equal, and demerol is deficient in psychic sedation.

Atropine is preferred to hyoscine or scopolamine, as the latter drugs often cause hallucinations and delusions in the aged.

Barbiturates are not used for premedication. Older patients are usually adapted better mentally and they approach surgery with little apprehension. Sedation as a safeguard against possible undue excitement is usually unnecessary and sometimes dangerous.

Spinal Technic

The spinal catheter is inserted through a Tuohy needle. The patient is placed in the lateral recumbent position with the legs flexed upon the abdomen as acutely as is physically possible. In the aged, the ideal position for spinal puncture is seldom attained. In case of injuries to the bones of the lower extremities, it is frequently impossible to move the patient to any great extent and seldom can he be moved from bed. The skin of the back is prepared with an antiseptic solution. A syringe equipped with a 24-gauge needle and containing 2 cc. of a 1 per cent procaine solution is used to raise a cutaneous wheal at the site of intended puncture. Ephedrine is eliminated from the local skin wheal to prevent a hypertensive state.

A 3½-inch, 16-gauge, Tuohy needle is inserted into the dural sac between L_2 and L_3. An attempt is made to introduce the needle at an angle of 45 degrees with the plane of the skin (fig. 1); this is frequently impossible in the aged. Bony changes and limited flexion may necessitate the use of the lateral approach for lumbar puncture. If the cerebrospinal fluid does not flow briskly when the stylet is removed, the needle should be turned on its axis through 360 degrees and gently advanced. Such manipulation causes the entire bevel of the needle to enter the subarachnoid space. The needle at this time is at an angle of approximately 25 to 45 degrees from the perpendicular with the skin and the bevel is directed cephalad. The plastic tubing (B-D No. 442T) is inserted. This angle, assisted by the internal curvature of the Huber point of the needle, causes the catheter to seek a cephalad direction in the intrathecal space.

If an obstruction is felt at the tip, the needle is turned 45 degrees in either direction and is then withdrawn a few millimeters until the catheter enters the intrathecal space. When the catheter is correctly placed, spinal fluid can be withdrawn by gentle aspiration with the 2 cc. syringe. Irrespective of site of operation or levels of anesthesia needed, the tubing should be inserted at least 5 cm. within the intrathecal space. For operation in the upper abdomen the catheter is inserted as far as 15 cm. When at the selected level, the needle is removed and the catheter is anchored to the skin at the site of lumbar puncture by adhesive tape. An adapter connects the plastic tube to a syringe (10 cc.) containing the anesthetic agent.

If any paresthesias are elicited while inserting the catheter, turning the needle through 45 degrees or twisting the catheter may carry the tip away from the nerve root and will permit the advance up the subarachnoid space. If paresthesias persist, further advancement must be abandoned and a seg-

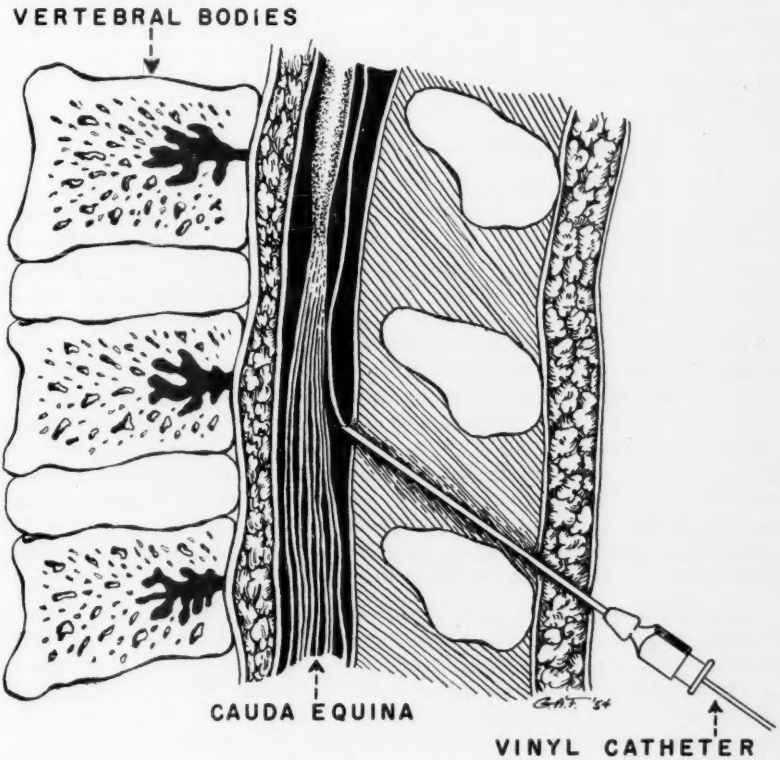

Fig. 1. A 3½-inch, 16-gauge, Tuohy needle is inserted into the dural sac between L_2 and L_3. An attempt is made to introduce the needle at an angle of 45 degrees with the plane of the skin.

mental type of anesthesia sacrificed. After the needle is removed but before the anesthetic agent is injected, slight withdrawal of the catheter prevents deposition of the anesthetic drug within a nerve sheath. The catheter never should be withdrawn through the needle,[3] since the needle's sharp edge may cut it off.

Intravenous Technic

Venoclysis is begun through an appropriate arm vein after the patient arrives in the operating room. A 15-gauge needle is preferable so that in case of hemorrhage, blood volume can be rapidly restored. The arm is held in the abducted position to be available for inspection and emergencies; however, care should be taken to prevent stretching the brachial plexus.

When a need for intravenous therapy during the postoperative care of the patient is anticipated, a plastic tubing may be substituted for the indwelling needle, since the tubing can be left in place for several days. Polyethylene tubing is nonirritating to the intima of the vein and the flexibility of the tubing allows free motion of the extremity. In the postoperative period the patient can assume many positions that would be denied him by an indwelling intravenous needle (fig. 2).

Administration of Spinal Anesthetic Solution

Procaine hydrochloride crystals (100 mg.) and pontocaine HCl (10 mg.) are diluted to 10 cc. with normal saline solution. Both of these agents have low coefficients of toxicity. The action of procaine alone is transient. Although pontocaine becomes effective slowly, its effect is prolonged.[4] This solution is considered approximately isobaric and is administered in units of 1 cc. If injection is made as slowly as possible, the jetlike stream that would be caused by forceful injection is avoided and the solution pools at the tip of the catheter. Anesthesia then is limited to a few segments of the spinal cord in either direction and does not diffuse up or down the spinal canal. One cc. (10 mg. procaine and 1 mg. pontocaine) constitutes the initial dose. Additional quantities of agent may be necessary to establish surgical anesthesia. However, for the aged patient the single initial injection frequently is sufficient not only to establish anesthesia but to maintain it for the whole operation.[5] Continuous spinal anesthesia, then, is not only practicable for longer operations, but the fractional-dose technic makes it particularly suitable for the aged and poor-risk patients. The advantage over classic single-injection spinal anesthesia is obvious.

Additional solution is administered only when indicated. The signs of waning anesthesia in a patient are loss of relaxation, restlessness, and finally evidence of discomfort. As these signs appear, an additional cubic centimeter of the anesthetic solution (10 mg. procaine and 1 mg. pontocaine) is injected. Maintenance doses are usually smaller than that dose which was necessary to initiate anesthesia,[6] and their action is usually more prolonged.

Lower Abdomen. Continuous spinal anesthesia lends itself well to surgery of the lower abdomen. If the lumbar puncture is made at L_2 to L_3 and the

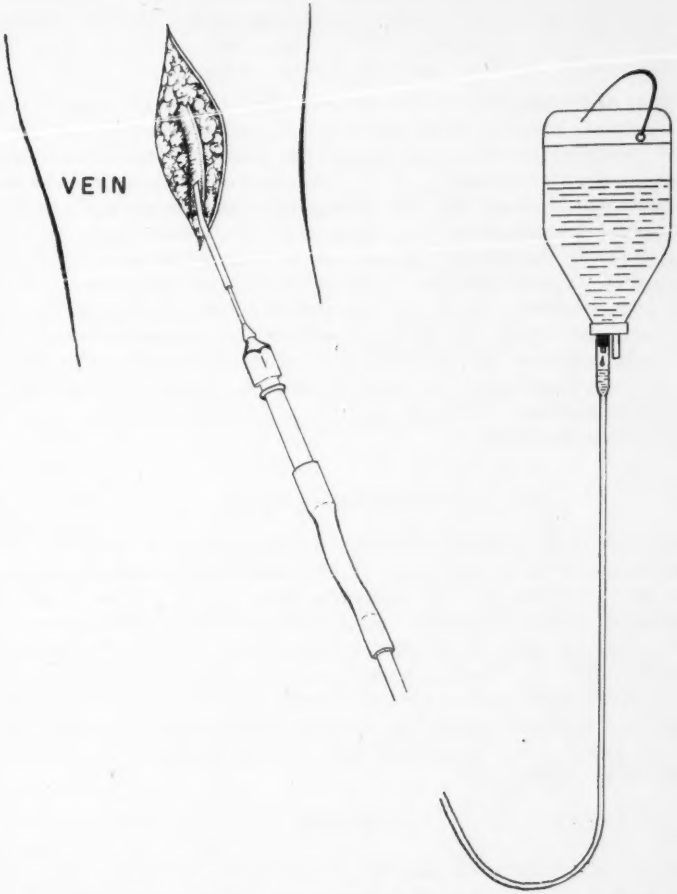

Fig. 2. Short length (5 inches) of polyethylene tubing size No. 190 is introduced into the vein through a cut down. Adaptation of the tubing to the venoclysis set is accomplished by an 18-gauge blunt cannula.

catheter threaded into the subarachnoid space for 5 cm., the area of sensory anesthesia is approximately T_8 to L_3. This segmental type of anesthesia permits operations in the lower abdomen but avoids loss of motor control of the legs. The hypotension so often seen in classic single-injection spinal anesthesia is absent. Relaxation of the anterior abdominal wall is adequate and analgesia is confined within the segmental limits.

Occasionally when the patient is placed in the lithotomy position as in a combined abdomino-perineal resection, the head of the table is tilted down.

Perineal anesthesia in this instance is obtained by using a hypobaric solution of pontocaine (10 mg.) in distilled water (10 cc.). Such a solution, being lighter than spinal fluid, will flow caudad to anesthetize the cauda equina.

Upper Abdomen. For ease of surgical manipulations in the upper abdomen, the catheter is threaded up the intrathecal space from 10 to 15 cm. and the level of anesthesia made to extend from T_5 to T_{10}. If care is taken to inject the solution slowly, a pooling of the agent will occur and delineation of the sensory component will be sharp. The sympathetic effect therefore is limited only to a few segments, because of the overlapping of the innervation in the sympathetic ganglia.[7] The hypotension which is usually pronounced in single-injection high spinal anesthesia either does not occur with this technic[4] or is slight and responds readily to vasopressors. The maintenance of tone in the leg muscles by absence of low motor anesthesia also prevents much of the hypotension seen in classic high spinal anesthesia. Nervous control of the skeletal muscles of the leg is lost only when the spinal agent is injected rapidly and in amounts larger than 1 cc. Complete sympathetic denervation is then accomplished and the hypotension which follows may be severe.

Supplementary Agents

Administration of additional agents is avoided if at all possible. The barbiturates are sometimes used to supplement spinal anesthesia. However, most of the aged patients enter the operating room calmly and peacefully. They seldom need additional narcosis. Pentothal is sometimes administered to control nausea, vomiting, and the discomfort of mesenteric traction. Banthine (50 to 100 mg.) controls the vomiting caused by intestinal manipulations, but it does not relieve the discomforts resulting from mesenteric traction. Nembutal subdues an excited patient more slowly but its action is much longer than that of pentothal; with either agent, dosages that may cause the patient to lose consciousness should not be administered.

SERIES

This series of 261 cases includes patients in the age range from 60 to 93 years (table 1). The operations performed ranged from abdominal and kidney

TABLE 1

Age Distribution of Patients

Age Range (yr.)	No. of Patients	Per Cent
60—70	180	68
70—80	75	30
80—90+	6	2
TOTAL	261	

operations to those on the lower extremities (table 2, a). Many of these patients (39 per cent) were considered poor surgical risks because of the presence of a disease in addition to that requiring surgery (table 2, b). Whenever possible a segmental type of continuous spinal anesthesia was attempted on this group. The results of the use of this type of high spinal anesthesia (71 cases) for surgery of the stomach and biliary system are particularly interesting (table 3). A segmental type of anesthesia from T_5 to T_{10} was attempted. Traction upon the stomach and esophagus caused nausea, vomiting, and discomfort that were not relieved by procaine infiltration of the vagus nerves. Banthine (50 to 100 mg. intravenously) allayed the nausea and vomiting that the patients experienced during manipulation in surgery of the biliary tract. In most instances, hypotension, if it appeared, was transitory, and not alarming. In all cases, it was easily corrected by the intravenous injection of neosynephrine in a dilution of

TABLE 2

Summary of 261 Cases

a. Site of Operation	No. of Cases
Upper abdomen	71
Lower abdomen	52
Colon	98
Lower extremity	36
Kidney	3
Hypotensive spinal	1
TOTAL	261

b. Risk	No. of Cases	Per Cent
Good	81	31
Increased	101	39
Unclassified	79	30
TOTAL	261	

c. Anesthetic Complications	No. of Cases
Nausea and vomiting	21
Hypotension	6
Spinal failure	6
TOTAL	33

d. Postanesthetic Complications	No. of Cases
Pulmonary complication	6
Headache	26
Nausea and vomiting	1
Mesenteric thrombosis	1
Hypotension	2
Cerebral vascular accident	1
Transfusion reaction	1
Death	6
TOTAL	44

TABLE 3
Upper Abdominal Operations
(Summary of 71 Cases)

a. Type of Operation	No. of Cases
Gallbladder and common duct	33
Cholecystojejunostomy	3
Abdominal exploration	12
Gastric resection	10
Gastroenterostomy	6
Subdiaphragmatic abscess	1
Pancreatic resection	3
Duodenal resection	1
Jejunal resection	2
TOTAL	71

b. Postoperative Complications	No. of Cases	Per Cent
Pulmonary	2	3
Mental or cerebral	1	1.5
Cardiac vascular	2	3
Gastrointestinal	1	1.5
Death	0	0
TOTAL	6	

c. Anesthesia—Risk	No. of Cases	Per Cent
Good	21	30
Increased	36	50
Unclassified	14	20
TOTAL	71	

0.2 cc. of a 1.0 per cent solution in 500 cc. glucose 5 per cent in water. The solution is permitted to flow rapidly (80 drops/min.).

Operations on lower extremities were most frequently for gangrene or fracture. In either case, the spinal catheter was inserted while the patient was still in bed. He was turned on the affected side for the insertion of the catheter and remained in this position while the initial dose was injected. Ten minutes was allowed to elapse for the spinal anesthesia to become fixed. With this analgesia, the patient was moved to the table and the manipulations of the extremity were painless.

In this series of 261 aged patients, there were no deaths attributable to the anesthesia. Six patients died within the first ten postoperative days (table 2, d).

The incidence of postspinal headache was low (10 per cent) probably because many of the patients classified as poor risks were unable to be ambulated and for that reason did not experience headaches.

The following two case reports are presented to illustrate the use of continuous spinal anesthesia for upper abdominal surgery in patients who are extremely ill.

Case Reports

Case 1. An 80 year old white man was admitted to the hospital on January 16, 1952, with a history of gastric ulcer since 1949. Physical examination revealed extreme cachexia, advanced arteriosclerosis, a blood pressure of 190/88, and a grade II systolic murmur.

On January 21, five days after admission, a gastric resection was performed under continuous spinal anesthesia. Premedication consisted of morphine 1/6 gr., atropine 1/150 gr. A plastic catheter was inserted 12 cm. cephalad from the third lumbar interspace in the subarachnoid space. After the surgical field had been completely draped, 1 cc. of a solution of pontocaine (1 mg.) was injected. Initial blood pressure was 190/88. The lowest pressure level was 156/84. The pulse rate ranged from 80 to 64 per minute.

The level of anesthesia was segmental and extended from T_3 to T_{10}. Sensory and motor control of the legs were unaffected. A total of 7 cc. of anesthetic solution was used over a period of three hours. Nembutal (50 mg. intravenously) was the only supplementary agent used.

The patient was discharged 14 days postoperatively after a relatively uneventful course.

Case 2. A 66 year old white woman was admitted in May 1952 for exploration of the common duct. Eight weeks previously she had become jaundiced. In 1944 she had been found to be diabetic; in 1943 she was found to have angina pectoris; and in 1950 she suffered a coronary occlusion.

Exploration of the common duct was carried out on May 20, 1952, under continuous spinal anesthesia. An indwelling plastic catheter permitted fractional dose injections of spinal anesthetic agents into the subarachnoid space at approximately 20 to 25 minute intervals. The solution of procaine (100 mg.) and pontocaine (10 mg.) in 10 cc. dextrose (5 per cent) was utilized. The initial injection of 2 cc. (procaine 20 mg. and pontocaine 2 mg.) caused an initial fall in blood pressure from 140/80 to 100/60 which was immediately corrected by neosynephrine drip (2.0 mg. in 500 cc. dextrose 5 per cent). The entire operation lasted 2¼ hours and required 7 cc. of anesthetic solution (70 mg. procaine and 7 mg. pontocaine).

The catheter was inserted 8 cm. from L_2. The upper level of sensory loss was at T_4 and the lower level was approximately at T_{12}. The patient could move her legs throughout the course of surgery.

The postoperative period was uncomplicated and the patient was discharged on the twelfth postoperative day.

Comment

The advantages of continuous spinal anesthesia are immediately apparent when the physiology and management of the anesthesia are thoroughly examined. Segmental areas of analgesia are produced by placing the tip of the catheter at the proper level and injecting small amounts of anesthetic agents. A narrow band of anesthesia is produced. The sympathetic denervation is minimal because the inosculating fibers in the ganglia reach to unaffected higher levels.

The disadvantages of continuous spinal anesthesia in the aged are: the difficulty of making the lumbar puncture, and possible danger of nerve trauma, and hemorrhage in the subarachnoid space. Not only are the lumbar punctures difficult to make as a result of vertebral bony changes but the patient frequently

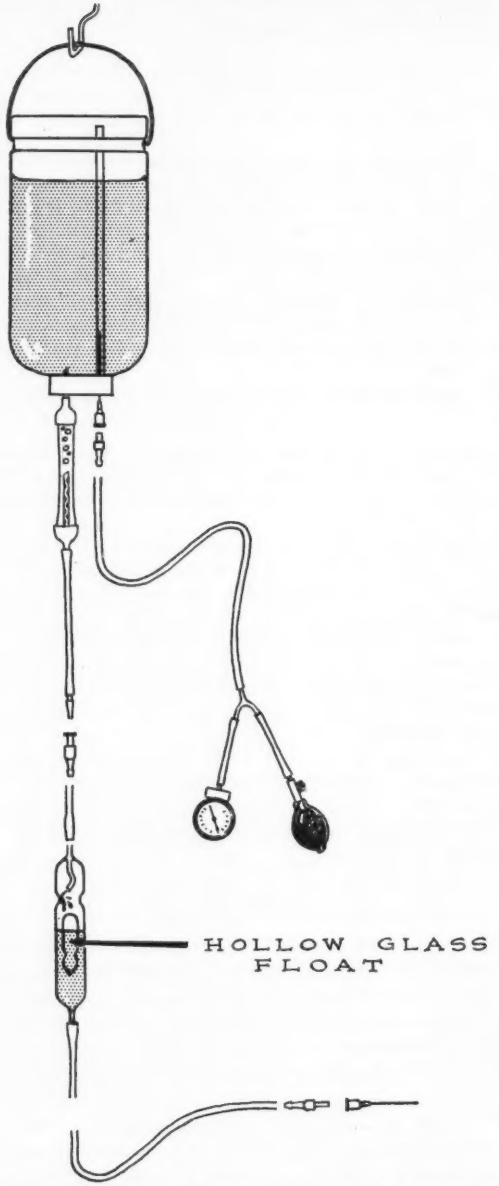

Fig. 3. Pressure infusion setup fitted to the 15-gauge needle to prevent air embolism.

cannot flex his legs upon the abdomen or cannot be removed from bed. The combination of all these factors sometimes forces the anesthesiologist to utilize the lateral approach.

Injury to the nerve roots is avoided by carefully threading the catheter to the desired level. The anesthetic agent must never be injected just after a paresthesia is elicited because the tip of the catheter may lie in the sheath of a nerve root. Spinal anesthetic agents if deposited within this covering may cause additional irritation to an already traumatized nerve.

The maintenance of anesthesia is accomplished by periodic injection of 1 cc. of mixture of the agent. The intervals between injections vary with each patient but not with age, weight, or sex.

The institution of a continuous spinal anesthesia in a patient who is desperately ill and in shock often brings about a noticeable improvement in his condition. Discomfort and pain are relieved and the patient frequently falls asleep from exhaustion. Limbs that were previously cold and clammy become warm and dry. The desperately ill patient appears to be in an improved state even before surgery is performed.

In the event of severe hemorrhage, when the replacement of blood loss is mandatory, pressure within the infusion bottle is sometimes necessary for the rapid transfusion of blood. Rather than risk the chance of air embolism, a pressure infusion setup (fig. 3) is fitted to the 15-gauge indwelling intravenous needle. Pressures (200 to 300 mm. Hg) sufficient to infuse the blood rapidly are applied. When the supply of blood in the bottle becomes exhausted, the air pressure still present is prevented from entering the blood stream by the MacIntosh safety dropper (modified by Hale). The float settles firmly into the ground-glass seat and seals the valve to prevent the passage of air. Such a setup allows the anesthetist confidently to turn his attention to other pressing matters in this critical period.

CONCLUSIONS

1. For the aged patient who is a poor surgical risk, a segmental type of continuous spinal anesthesia is appropriate because it offers a band of sensory anesthesia at the site of incision, profound relaxation of the musculature, and minimal interference with the sympathetic nerves. The absence of profound blood pressure changes in high continuous spinal anesthesia is attributable to the segmental type of analgesia provided and to the special anatomy of the fibers extending up the sympathetic chain.

2. The plastic-catheter technic is recommended because it allows the anesthetic agent to be deposited at any preselected level of the subarachnoid space.

3. A series of 261 cases is reviewed which includes patients operated upon at ages ranging from 60 to 93 years. Thirty nine per cent of these patients were considered poor surgical risks. Whenever possible a segmental type of continuous spinal anesthesia was attempted in this latter group. Of the six postoperative deaths, none was attributable to the anesthesia.

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KERATOACANTHOMA: HISTOPATHOLOGIC CRITERIA FOR DIAGNOSIS

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KERATOACANTHOMAS appear as firm, white, keratotic nodules on the skin of the face or of the dorsum of the hand. They are characterized by rapid growth to maximum size and benign biologic behavior. On microscopic examination, under high-power magnification they possess some of the features of low-grade, superficial squamous cell carcinoma, and under low-power magnification they resemble to a degree molluscum contagiosum.

The disparity between the architecture and the behavior of keratoacanthomas has attracted the worldwide attention of dermatopathologists who have proposed numerous descriptive names for the lesions. For the most part their nomenclature reflects the superficial, benign nature of this group of tumors. Freudenthal[1] first suggested "keratoacanthoma"; MacCormac and Scarff[2] in their report of ten cases suggested "molluscum sebaceum"; and Poth[3] suggested "tumor-like keratoses." A recent LANCET editorial[4] noted the 76 cases described by Beare[5] and suggested the name "molluscum pseudocarcinomatosum."

In an effort to establish definitive histopathologic criteria as a basis for the diagnosis of keratoacanthoma, we undertook a comparative histopathologic study of the biopsy specimens from the 14 cases of the lesion seen here since 1948.

Materials and Methods

Of approximately 42,000 surgical specimens screened for the presence of low-grade squamous-cell epitheliomata, 377 qualified; however, only 14 of the latter were lesions with both the macroscopic and the microscopic findings consistent with a diagnosis of keratoacanthoma.

Clinical Features

The diagnosis of keratoacanthoma was confirmed in ten men and four women. In seven patients the lesions occurred on the hand or wrist, and in the remaining seven they were present on the face: ear (two), lip (two), jaw (one), nose (one), and forehead (one). The ages of the patients ranged from 51 to 73 years, the average age being 59 years; eight patients were in the sixth decade. Five patients had associated or unrelated dermatologic complaints. The lesions had been present from four weeks to nine months, and were variously described

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TABLE

Data on 14 Patients Having Keratoacanthoma

Age (yr.)	Sex	Site of Lesion	Duration of Lesion	Associated Skin Lesions	Treatment	Follow-up Period (mo.)
51	M	Hand	3 mo.	Contact dermatitis	Excision	None
52	F	Left hand	5 mo.	None	Excision	52
52	M	Wrist	2 mo.	Previous excision similar nodule	Excision	27
53	F	Hand	Not known	Contact dermatitis	Excision	1
53	F	Skin behind ear	4 mo.	None	Excision	18
53	M	Forehead	2 mo.	None	Excision	18
58	M	Jaw	4 mo.	None	Excision	31
58	M	Wrist	2 mo.	Infectious eczematoid dermatitis	Excision	7
63	M	Hand	9 mo.	None	Excision	31
63	M	Lower lip	6 wk.	None	Excision	14
64	M	Lip	1 yr.	None	Excision	46
71	M	Ear	2 mo.	Epithelioma of hand treated by x-ray 1941	Excision	9
72	M	Hand	Not known	None	Excision	67
73	F	Nose	4 mo.	None	Excision	3

by different observers as white, firm, hard, round, well-demarcated, warty, keratotic, crusted or scaled nodules that were about the size of a pea. All of the lesions were treated by surgical excision. No recurrences were noted in 13 patients followed from 1 to 67 months; in one patient there was no follow-up (table).

Histopathology

The lesion was characterized histopathologically by: (1) projection above the plane of the adjoining epidermis; (2) hyperkeratosis of the adjoining epidermis; (3) a central crater, with overhanging edges in some instances; (4) pseudo-epitheliomatous hyperplasia marginally and acanthotic, squamous-cell carcinoma-like nests centrally; and (5) a slight-to-moderate chronic inflammatory reaction in the surrounding corium. In addition, the squamous-cell nests contained prominent intercellular bridges, central keratinization, little central necrosis, and few mitotic figures. Periodic acid-Schiff stain[6] failed to reveal the presence of fungi. However, the cells of the stratum granulosum and the squamous-cell nests contained prominent, cytoplasmic, periodic acid-Schiff positive granules. In contrast most of the cells of the squamous-cell nests in overt carcinomas did not contain such granules. The most significant points differentiating them from squamous cell carcinomas were:

(A) The central crater and verruciform appearance.
(B) The superficial resemblance to molluscum contagiosum.
(C) The completely differentiated appearance of the hypertrophic squamous-cell elements.

(See figures 1, 2 and 3).

DISCUSSION

The concept of benign, squamous-cell carcinoma-like lesions of the skin is not new, but it rarely has been discussed in the American literature. In 1936, MacCormac and Scarff[2] reviewed ten cases of molluscum sebaceum that were easily eradicated by excision or the use of CO_2 pencil; they described the nodule as a hemisphere that remains stationary in size (approximately that of a small nut), is centrally depressed and has an adherent scale. They reported that the lesion occurred with equal frequency in both sexes.

Poth[3] excellently described a case of tumor-like keratoses that occurred as multiple nodules on the skin of the hand following exposure to sun and sea water. Grossly, the tumor appeared round, firm, translucent, and pearly. Tissue sections were examined by a number of pathologists whose diagnoses varied: "exuberant verruca vulgaris" (H. Montgomery); "dyskeratosis and hyperkeratosis" (U. J. Wile); and "squamous-cell carcinoma, Grade I" (R. C. Wanstrom and G. H. Belote). Discussing Poth's case, Montgomery calls attention to the presence of epithelial proliferation and regular pearl formation in other instances of pseudo-epitheliomatous hyperplasia, including bromoderma, blastomycosis, and the edges of nodular ulcerative syphiloderm. Wile's description of the histopathologic changes in this case is exceptionally clear, and

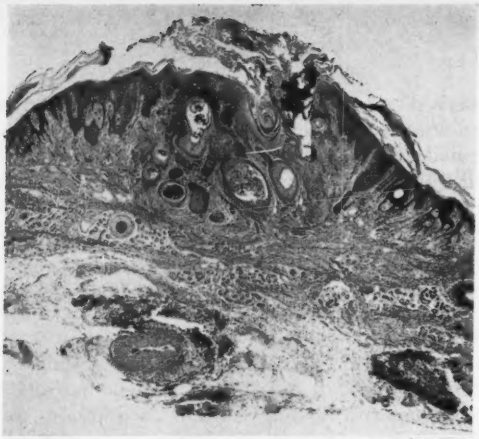

Fig. 1
(X 14)

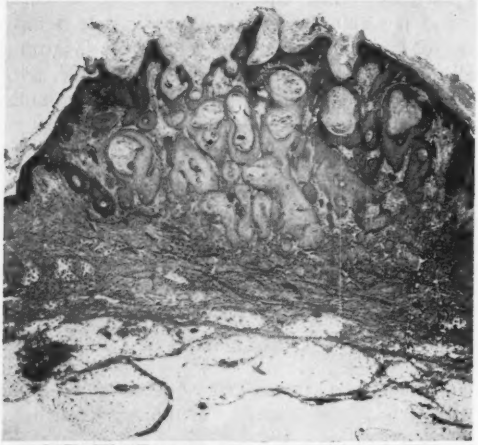

Fig. 2
(X 9)

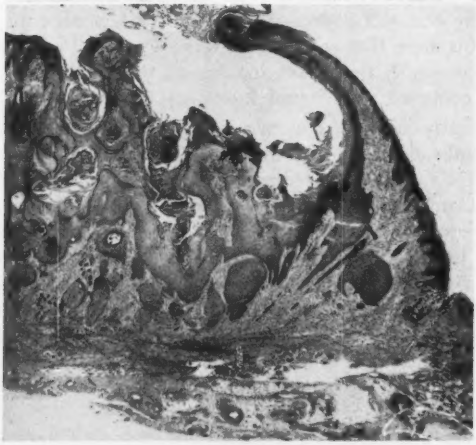

Fig. 3
(X 14)

Figs. 1, 2, and 3. Three examples of keratoacanthoma. Note central crater and verruciform appearance, molluscum architecture, and well-differentiated squamous-cell elements.

illustrates the marked degree of differentiation of the lesion by noting the conspicuousness of the stratum granulosum, and the large prickle cells with well-exhibited spines. In Poth's case all of the tumors involuted spontaneously eight months after their appearance; no treatment was instituted.

Beare[5] in reviewing 76 cases of molluscum sebaceum pointed out that the stretched epithelium in the outer area of the tumor tempts one to make a diagnosis of malignancy.

The etiology of the lesion is not known. Attempts to demonstrate inclusion bodies or fungi have been unsuccessful in our cases. Poth could not transmit the tumor to laboratory animals, nor could he reproduce it in a patient by cutaneous innoculation of extracts of tumor. A viral etiology has not been established.

The prognosis is always excellent, and the lesions have never been known to recur, as cited by Poth,[3] Smith,[7] Musso and Gordon.[8] The clinical observation of the limited growth potential of these rare lesions, their benign and at times regressive course indicate they are separate and distinct from squamous cell carcinoma. The term *keratoacanthoma* is an appropriate designation. The diagnosis can be established on the basis of the histopathologic criteria set forth.

SUMMARY

The clinical and histopathologic findings in 14 cases of keratoacanthoma are presented. The lesion, which is similar to "molluscum sebaceum" or "molluscum pseudocarcinomatosum" described in the British literature, is a benign squamous-cell growth of unknown etiology. It is characterized by a verruciform appearance and a superficial resemblance to the lesion of molluscum contagiosum. Histologic features of differentiation from squamous cell carcinoma are outlined.

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FIBROUS DYSPLASIA OF BONE

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THE significance of "fibrous dysplasia of bone," a relatively recent addition to medical nomenclature, still remains obscure. The term is used to designate certain specific osseous lesions often subclassified into three main types, depending upon their anatomic distribution and their association with other extraskeletal anomalies. In type I, the monostotic, the lesions are single or multiple but are confined to one bone; in type II, the polyostotic, the lesions involve more than one bone; in type III, the lesions are widely disseminated throughout the entire skeleton, although unilateral preponderance is often seen.

In type III fibrous dysplasia of bone, common accompaniments are cutaneous pigmentation and, especially in females, precocious puberty. Albright and his associates[1] were the first to demonstrate this relationship clearly. Their published report in 1937 stimulated interest in this curious anomaly and led to its recognition as an established clinical entity; thus, the disorder is often referred to as "Albright's brown-spot syndrome." Other descriptive terms have been used, such as "pseudohyperparathyroidism" and "osteitis fibrosa cystica without hyperparathyroidism."

For all three types the current trend, as suggested by Lichtenstein and Jaffe,[2] is toward the use of the general heading, "fibrous dysplasia," since in all three types there is striking roentgenologic and histologic similarity among individual lesions. We shall use this term and shall try to justify its use from the evaluation of our own experiences with the pathologic state it designates.

CLINICAL STUDY

A survey of our records for the past 25 years disclosed 11 cases in which the clinical, roentgenologic or histologic features were sufficiently characteristic to justify the diagnosis of fibrous dysplasia and also to designate the extent of the disease. Findings in the 11 cases are briefly outlined in the table. There were six additional cases exhibiting the typical microscopic criteria; these were not included in our study since adequate roentgenographic skeletal surveys were not available.

Of the 11 patients considered, 8 had extensive skeletal involvement, in one of whom it was predominantly unilateral. In the remaining three cases the lesions were confined to the femur and tibia of the same side, a strikingly monomelic distribution.

Although 6 of these 11 patients were more than 30 years of age when

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initially seen, 8 had a long-standing history of osseous derangement dating back to childhood, and 6 of them had sustained major fractures.

Of the entire group only one, a 19 year old girl, had a history of precocious puberty. She had a severely rarefied skeleton and at the age of seven years had pubic and axillary hair, accelerated somatic development, and onset of menstruation. No pigmented areas were noted.

Two patients had extensive pigmentation; characteristically this was accompanied by widespread bone disease.

Two of the patients had had hyperthyroidism that had been corrected by subtotal thyroidectomy. The unusual association of fibrous dysplasia and hyperthyroidism has been mentioned in the past by others.[2,3]

Another of the 11 patients had two parathyroid explorations under the erroneous impression that the bone disease might be due to hyperparathyroidism. These operations were performed in the early 1930's prior to the original descriptions by Albright and associates. It can now be fully appreciated that parathyroid tumors are unrelated to this particular malady and hence parathyroid explorations are no longer justified.

SYMPTOMS AND SIGNS

Because major functional disabilities in fibrous dysplasia arise from skeletal defects, its symptomatology is primarily that of skeletal dysfunction. In types I and II, where the lesions are frequently single and never widely disseminated, there are few, if any, symptoms. The importance of their occurrence is often confined to the diagnosis of an observed roentgenologic defect in one or two bones. We shall confine the remainder of our discussion largely to the disseminated form of the disorder, since it is in this type that the other clinical features appear.

Persistent dull pain in the extremities, particularly the legs, is a frequent complaint of patients with fibrous dysplasia, and was the presenting symptom in more than half of our cases. A pathologic fracture may offer the first indication of the disease. When the lesions are widespread, the fractures are sometimes multiple or recurrent. One of our patients suffered fractures of the sternum, both clavicles, both femora, and nine ribs, in a period of nine years.

Often the onset of symptoms is more insidious. The involved skeletal part may have the appearance of a deformity with obvious local enlargement that is due either to bending or to expansion of the bone. An antecedent history of trauma without a genuine fracture can sometimes be traced in such instances. Actual lengthening of a limb may occur; however, with marked and progressive involvement, shortening of the extremity is more likely. A troublesome limp and gait disturbance may subsequently develop. The osseous changes with the resulting distortions usually progress slowly until skeletal growth terminates with the advent of puberty. At this time there is ordinarily a definite cessation of the pathologic process in the bones. However, the patient may become permanently crippled if both legs have been significantly affected.

In type III, the skull is frequently the site of a major localization of the

TABLE

Analysis of 11 Cases Diagnosed as Fibrous Dysplasia of Bone

Case No.	Age (yr.)	Sex	Duration (Known Years)	Skeletal Involvement	Presenting Complaint or Problem	Pigmentation	Ca-P	Phosphatase	Biopsy	Fractures	Remarks
1	31	M	23½	Widespread	Leg pains. Facial asymmetry.	Extensive	Normal	4.25	None	14	Parathyroid exploration (twice).
2	37	M	31	Extensive	Pain left leg with bowing.	None	Normal	7.6	Yes	8	Lesions predominantly left-sided (femur, tibia, ilium, 2 tarsal and one metatarsal bones and 10th rib). Skull and 10th dorsal vertebra implicated bilaterally.
3	57	F	Noted in routine chest film in 1941.	Extensive	Symptoms of hyperthyroidism for 8 yr.	None	Normal	5.3	Yes	None	Thyroidectomy.
4	48	M	36	Extensive	Bilateral blindness-3 weeks' duration.	None	Normal	12.0	None	3	At age of 12 yr. difficulty breathing through left nostril. Overgrowth of all bones left side of face and forehead.
5	27	F	4	Left tibia and femur	Pain in left leg.	None	Normal	2.4	Yes	1	

TABLE — (Continued)

Case No.	Age (yr.)	Sex	Duration (Known Years)	Skeletal Involvement	Presenting Complaint or Problem	Pigmentation	Ca-P	Phosphatase	Biopsy	Fractures	Remarks
6	18	F	16	Extensive	Pain in right leg.	None	Normal	15.4	Yes	5	
7	26	F	5	Right tibia and femur	Recurring pain right knee and leg.	None			Yes	None	
8	60	F	Over 50	Extensive bilateral	Soreness and pain both legs.	None	Normal	12.5	Yes	1	Vertebral involvement since childhood with marked kyphosis. Thyroidectomy 5 yr. previously.
9	33	F	21	Right tibia and femur	Tiredness, irritable colon.	None	Normal	1.5	None	1	Pathologic fracture of right femur at age of 12 yr.
10	18	F	18	Extensive	Obesity.	Present	Normal	14.1	None	None	Marked asymmetry of head present since birth.
11	19	F	14	Extensive	Pain in right arm, at side of pelvis, and right ribs.	None	Normal	5.2	None	8	Menses and secondary sex characteristics appeared at age of 7 yr.

disturbance. When the skull becomes involved, the cranial tables usually reveal sclerosis and thickening as well as areas of rarefaction. This is in striking contrast to the events in hyperparathyroidism in which cranial thickening is not observed. Facial asymmetry may develop, due to unilateral bony overgrowth; frequently it is the only visible stigma of the disease. Occasionally, grotesque and hideous deformities are produced, and these probably account for most examples of so-called leontiasis ossea. Involvement of the roof of the orbit may result in considerable downward displacement of the eyeball and is a rare cause of unilateral exophthalmos. Disease of the sphenoid wings may lead to compression of one or both optic nerves with consequent optic atrophy and blindness. This was the presenting problem in one of our cases (case 4). The patient, a 48 year old man, had noted the onset of bilateral blindness three weeks prior to examination. However, the history revealed that at the age of 12 years he had begun to have difficulty in breathing through the left nostril (thickening of left nasal bones) and showed progressive facial asymmetry. He had sustained two femoral fractures during childhood. Widespread skeletal involvement was revealed at the time of initial examination.

Similar morbid processes may result in varying degrees of deafness caused by encroachment upon the auditory apparatus.

Of interest is the case reported by Neller[4] in which the patient was operated upon, for, presumably, an infected cyst of the scalp. The lesion proved to be a herniation of the meninges through a cranial osseous defect produced by fibrous dysplasia.

Pigmentation: Cutaneous pigmentation is the most common extraskeletal manifestation of this condition. Lichtenstein and Jaffe[2] in 1942 reported an incidence of 35 per cent. In our review of about 100 cases reported since then, 63 per cent of the patients exhibited this abnormality. The higher incidence may be partly due to a more careful scrutiny by examiners as a result of their increased awareness of the clinical relevance of pigmentation. Jaffe[5] emphasized how readily these colored patches can be overlooked unless a meticulous examination, particularly of the scalp, is carried out. These flat spots are yellowish or yellowish-brown in color (cafe-au-lait), and reflect accumulations of abnormal amounts of melanin in the basal cells of the epidermis. The pigmented area may consist of a small uniform patch or it may cover a very extensive field. The edges are typically serrated and have been described by Albright as "irregular as the coast of Maine when compared to the coast of California."

Skeletal Precocity: In many cases there is hastening both of skeletal growth and of maturation; occasionally skeletal maturity occurs without sexual precocity. The aberration results in a child's becoming exceedingly tall for his age and manifesting epiphysial development far in advance of the chronologic age. However, these persons ordinarily reveal a premature arrest of growth and may eventually appear of shorter stature than average because of the accelerated ossification and fusion of the epiphyses.

Sexual Precocity: This is noted in 20 to 30 per cent of all cases. The incidence of sexual precocity has probably been overestimated because of the

spectacular nature of the symptoms as compared with those due to skeletal anomalies or pigmentation.

The early puberty is almost invariably seen in females; however, several instances of its occurrence in males are on record.[6, 7] Its etiology is unknown. Stimulation of the hypothalamus by pressure from an adjacent fibrodysplastic lesion has been suggested as a cause. The scant autopsy material available fails to shed any light on the problem. From a purely functional standpoint, it appears to be an early "awakening" of the pituitary.

Blood Chemical Findings: An elevated alkaline phosphatase concentration is the only repeatedly abnormal laboratory finding and in some, it too is normal. The concentration tends to parallel roughly the degree of skeletal rarefaction. Blood calcium and phosphorus determinations and urinary and fecal calcium excretions are characteristically within normal range; these contrast with the deviations usually encountered in hyperparathyroidism.

Roentgenologic Findings

The lesions in all three types of fibrous dysplasia present a fairly typical roentgenographic appearance. If a number of bones are involved, the roentgenographic evidence is so unmistakable that the diagnosis can be made on this basis alone. In no other pathologic entity is there as decided a tendency towards monomelic and unilateral skeletal involvement. Even when both sides are extensively involved, there usually, though not always, is a predominance of the lesions in one side of the body. Curiously, the pigmentation shows a similar tendency to homolateralization.

The histologic features of bony lesions in fibrous dysplasia may account in part for the roentgenologic appearance of the lesions. The lesions consist essentially of masses of fibrous tissue in which are found numerous scattered spicules of metaplastic bone. While this cellular mass is often seen beneath the periosteum, the commonest site is in the medullary portion of the bone. The latter results in resorption and thinning of the cortex from within with a concurrent outward expansion as mentioned earlier. Bowing and fractures can readily occur through these weakened areas. On the other hand, considerable ossification of the connective-tissue substratum may take place, and on the roentgenogram this may be observable as a homogeneous density, described as of a "ground-glass" or "smudged" appearance.

The following roentgenographic features have been considered valuable diagnostic criteria:[5, 8-10]

(1) A well-demarcated radiolucent area within a bone.

(2) Usual localization of the lesion in the diaphysis when a long bone is attacked.

(3) Presence of normal osseous fabric between lesions.

(4) "Smudged" or "ground-glass" appearance due to intrinsic calcification. Usually observed in the medullary portion of the affected long bones.

(5) Ridge formation and trabeculation suggesting cystic changes and often producing a multilocular appearance. (Actually, cyst formation seldom occurs and when found it is the result of focal degeneration of, or hemorrhage into, the fibrodysplastic tissue.)

(6) Broadening or expansion of the cortex with frequent marked deformities.
(7) Absence of periosteal reaction except in the presence of a pathologic fracture.
(8) Osteosclerotic skull lesions (besides rarefaction) with consequent disfigurement.
(9) Frequently accelerated osseous growth in childhood with early epiphysial closure and resulting dwarfism or deficient stature.
(10) Pathologic fractures with frequent shortening and gross distortion of bone.

ETIOLOGY AND HISTOPATHOLOGY

According to Lichtenstein and Jaffe,[2] the histologic peculiarity of polyostotic fibrous dysplasia seems to be a "disturbed function or development of the bone forming mesenchyme" which normally is the origin of the myeloid or fatty marrow. This dysfunction results in the substitution of the osseous medulla by a peculiar cellular aggregate consisting primarily of connective tissue frequently arranged in interlacing bundles and whorls. Within this fibrous tissue are varying numbers of trabeculae of partly calcified, newly formed, primitive bone. Islands of cartilage can be seen in some of the sections. Groups of multinuclear giant cells closely resembling osteoclasts are often noted in the neighborhood of blood vessels or of hemorrhages. Microscopic study reveals that bone trabeculae and the adult cartilage are formed by the direct metaplasia of the undifferentiated fibrous or mesenchymal (reticuloendothelial) tissue. Mature collagenous connective tissue can be seen to form by enlargement and collagenous transformation of pre-existing and newly formed reticular fibrils.

Since these pathologic oddities are seen so frequently in early childhood, Lichtenstein and Jaffe[2] envisioned a congenital basis for the anomaly.

Valls, Polak and Schajowicz,[11] using special stains for embryonal tissue, were able to confirm Lichtenstein's earlier observations. They emphasized that the presence of large cartilaginous masses growing in plain mesenchyme was strong evidence favoring the congenital origin of this dysplastic tissue. These masses, however, were only observed in the polyostotic form of the disease, which they accepted as a real dysplasia. The absence of the cartilaginous masses from the monostotic or solitary type cast doubt on the latter's congenital origin and on the possibility of an etiology common to the polyostotic form. The authors asserted that monostotic lesions may correspond to the final cicatricial stages of inflammation or traumatic processes. They admitted that the problem of etiology is a difficult one and at the present time is not settled.

Schlumberger,[12] after a review of 67 cases of monostotic fibrous dysplasia studied at the Armed Forces Institute of Pathology, concluded that the lesions of the polyostotic and monostotic forms of the disease are produced by different etiologic factors. He expressed the belief that many monostotic lesions probably represent an abnormal response to bone injury. He was unable to find islands of cartilage in any case of his series except in connection with healing pathologic fractures.

As the most logical etiologic mechanism, Albright postulated that the disease is a dysfunction of the central nervous system primarily localized in the region

of the hypothalamus. In his view such a disturbance would best explain widespread and seemingly unrelated lesions which involve simultaneously the skin, the skeleton, and the endocrine glands.

DIFFERENTIAL DIAGNOSIS

A. Polyostotic form:

1. The importance of the exclusion of hyperparathyroidism in the differential diagnosis has already been mentioned; convincing proof is offered by the relatively high percentage of unnecessary explorations for parathyroid adenomata in cases subsequently diagnosed as fibrous dysplasia.

The differentiation between the two disorders is not usually difficult to make. When precocious puberty and extensive skin pigmentations are present there should be no uncertainty. In incomplete forms of the disorder it is well to remember that hyperparathyroidism is rare in childhood, in which fibrous dysplasia usually becomes manifest. In the latter ailment there usually is no constitutional symptomatology; the patients ordinarily feel well except for the skeletal disabilities. In hyperparathyroidism patients are frequently distressed with severe muscular weakness, digestive disturbances, and renal lithiasis and nephrocalcinosis which often result in renal failure.

The skeletal system in parathyroid disease may show widespread osteoporosis without osteosclerosis. Resorption of the periodontal lamina dura is common. In fibrous dysplasia the osseous defects are spotty in character with roentgenologically normal bone between them. The thickening of cranial tables with cephalic asymmetries, the condensation of the long bones with the resulting "ground-glass" appearance in association with a consistently noninvolved lamina dura are features never noted with parathyroid hyperfunction.

Finally the characteristic hypercalcemia and hypophosphatemia with negative calcium balance of hyperparathyroidism contrast with the normal values seen in fibrous dysplasia.

2. Skeletal enchondromatosis (dyschondroplasia or Ollier's disease) begins early in life and is associated with dwarfism and exceptionally may be predominantly unilateral thus resembling fibrous dysplasia. However, in cases of skeletal enchondromatosis there is a characteristic involvement of the bones of the hands and feet by cartilaginous exostosis giving rise to a typical punched-out appearance with bulging of the contours visible on the roentgenograms. Since only bones ossified in cartilage are affected in Ollier's disease, rarefaction of the skull is extremely rare. Disturbances of the epiphyses are a prominent finding in cases of skeletal enchondromatosis, and are not observed in those of fibrodysplastic anomalies. Sexual precocity and cutaneous pigmentation are additional factors helpful in the differentiation since they are never identified with Ollier's disease. The latter's distinctive histologic picture, which is basically hyaline cartilage, should settle any remaining diagnostic indecision.

3. Hand-Schüller-Christian disease (lipoid granulomatosis) is sometimes mistaken for fibrous dysplasia when skull roentgenograms reveal radiolucent areas. Distinguishing points are the frequent occurrence of diabetes insipidus

and abnormally high blood cholesterol levels and the absence of osteosclerosis, cutaneous pigmentation and sexual precocity in the xanthomatous bony disorder as compared to polyostotic fibrous dysplasia. Occasionall, a biopsy becomes necessary for differentiation; the presence of an abundant number of foam cells establishes the presence of xanthomatosis.

4. Neurofibromatosis with skin pigmentation frequently exhibits rarefied osseous areas and consequently assumes importance in the differential diagnosis. However, in neurofibromatosis the defects of bone are not extensive and fail to reveal sclerosis. They are usually restricted to certain regions of the skeleton, such as the upper end of tibias and lower ends of femurs. The pigmented areas have smooth edges as compared to the irregular margins commonly discernible in fibrous dysplasia.

5. Multiple myeloma may at times have to be strongly considered. This more ominous state is almost never seen in patients less than the age of 40 years. The following distinguishing traits are commonly recognized: elevated serum protein and calcium levels, Bence Jones proteinuria, plasma cells in the peripheral blood and a characteristic marrow histology. Renal calculi, renal dysfunction, and anemia are commonly associated serum findings. Alkaline phosphatase is usually normal.

6. In sarcoidosis the osseous lesions are usually confined to the hands and feet. The frequently accompanying granulomatous patches involving the skin, lymph nodes, parotid glands, uveal tract, and lungs, the hyperproteinemia and hyperglobulinemia and the palsies of the seventh and other cranial nerves should clarify the diagnosis. Occasionally, when these features are missing a biopsy is required to differentiate sarcoidosis from fibrous dysplasia.

7. Paget's disease, granulosa-cell tumors of the ovaries with precocious puberty, and metastatic bone malignancies rarely cause any confusion and deserve only passing mention.

B. Monostotic form:

Until a clarification of the etiology of monostotic fibrous dysplasia is definitely achieved, it would probably be wise to consider it a milder grade of the polyostotic form, as Lichtenstein originally suggested. The lesion or lesions of this type of fibrous dysplasia are much more difficult to identify on clinical and roentgenologic grounds alone than are those of the polyostotic type.

It is interesting to note that of the 67 monostotic cases reported by Schlumberger[12] in 1946, the correct diagnosis was not given once in the roentgenographic report before the histologic studies were completed. In only 19 cases was the lesion recognized as fibrous dysplasia by the pathologists who submitted the specimens to the Armed Forces Institute of Pathology.

Of the long list of solitary lesions that are apt to cause diagnostic difficulties, simple cysts, giant-cell tumors and nonosteogenic fibromas are among the commonest.

Solitary bone cysts characteristically occur in the metaphysis of long bones, particularly the humerus, femur, and tibia, in contrast to fibrodysplastic tissue which is prone to develop in the diaphysis. The cysts produce resorption with

expansion of the bone and thinning of the cortex, but the osseous condensation seen in the other condition is always lacking.

Giant-cell tumors are ordinarily found in an older person; they tend to be located close to the epiphyses and produce a multicystic, trabeculated appearance in the roentgenogram, as if the mass were composed of large bubbles. There is no intrinsic calcification demonstrable. Moreover, these tumors exhibit a strikingly favorable response to irradiation.

Nonosteogenic fibromata possess no distinguishing features except for the absence of thickening of bone.

Usually a tissue biopsy is essential to ascertain the true nature of these monostotic lesions.

PROGNOSIS AND TREATMENT

The outlook for the great majority of patients with fibrous dysplasia of bone is very good and their life expectancy is normal. A few die of their disease, but these patients are those who have been burdened with extensive skeletal disease from an early age and, especially those with significant endocrine dysfunction. Considerable slowing and actual arrest of the morbid osseous processes ordinarily occurs with the advent of skeletal maturity.

Therapy in this disorder calls for a great deal of individualization. Only those areas causing or apt to cause trouble require attention. These are often located in the upper end of the femurs and in the long bones generally. Thorough curettage of the unhealthy tissue and filling of the resulting cavity with autogenous bone chips is an effective method of eradicating the disease locally and strengthening the osseous structure. The entire lesion should be resected; otherwise, its recurrence after absorption of the grafted chips is to be anticipated.

If a bone has undergone one or more fractures or is in danger of fracturing, the introduction of a large graft may be particularly helpful. Nonoperative therapy, such as braces and corsets, is also indicated for support or correction of deformities. Patients should be cautioned as to the proper use of the involved skeletal part in order to prevent fractures.

SUMMARY

1. Some of the clinical, roentgenographic, and histologic features of fibrous dysplasia of bone are presented as a basis for a review of the subject of fibrous dysplasia with special emphasis on its diagnosis and differentiation from other osteolytic diseases, particularly hyperparathyroidism.

2. Some of the present thoughts on the controversial issue of the etiology of the monostotic variant and its relationship to the polyostotic form are briefly discussed.

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CONTROLLED HYPOTENSION IN THE SURGICAL TREATMENT OF CERTAIN CASES OF PATENT DUCTUS ARTERIOSUS

Report of Four Cases

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THE surgical treatment of patent ductus arteriosus is well established and is indicated in almost every case. Usually it is not technically difficult, particularly in children. However there are certain cases, mostly in adults, in which the operative procedure is fraught with technical difficulty and hazard. These cases are complicated by degenerative vascular disease or unusual anatomic configuration of the ductus and adjoining vessels. The vessel walls about the ductus may have undergone changes caused either by cystic medial necrosis or by subacute endarteritis; calcium deposits may have formed beneath the intima. Large ducti may be associated with hypertension and secondary aneurysmal changes in the pulmonary artery. Occasionally a ductus may be of large caliber and short length, resembling an aortic pulmonary window more than a persistent vessel that communicates between the aorta and pulmonary artery. Whenever one or more of these features are present, the ductus is no longer a pliable plastic vessel that is amenable to safe surgical closure. Furthermore, the danger of uncontrolled hemorrhage increases directly with the degrees of vascular degeneration and pulmonary hypertension.

Controlled hypotension during surgery is an established technic that has proved of considerable value in conditions where frank hemorrhage or troublesome oozing is anticipated.[1-3] It has been most widely used by neurosurgeons and those surgeons doing extensive abdominal operations for advanced carcinoma. It not only reduces hemorrhage but shortens operative time. However, it certainly is a procedure not to be undertaken lightly and has definite contraindications including severe anemia, disease of the coronary arteries and renal disease.

Our interest in applying the technic of controlled hypotension to surgery of patent ductus arteriosus was stimulated by the fatality that occurred in the operating room, which is briefly described.

The patient was a 23 year old man in whom the diagnosis of an enormous patent ductus arteriosus with pulmonary hypertension had been established by the usual diagnostic procedure and cardiac catheterization. At operation, a

ductus measuring 3.8 cm. in diameter and only 1 cm. in length was encountered. The pulmonary artery at its bifurcation measured 7 cm. in diameter. The aorta, which had a fusiform dilatation at the ductus, was completely mobilized above and below to increase the degree of control, and a very large Potts-Smith type of clamp, especially devised for this case, was applied to the aortic end of the ductus. Following occlusion of the sclerotic ductus, a rent appeared in the aneurysmal pulmonary artery, and in spite of all efforts to control the hemorrhage, the patient died. Extreme vascular degeneration with notable increase in intraluminal pressure was the major factor in this case.

Since then, we have utilized controlled hypotension in four patients having complicated patent ductus arteriosus. We are in complete agreement with Glenn[4] that the procedure is an extremely valuable adjunct in this type of operation. In all four cases hypotension was induced by arteriotomy with controlled bleeding. We have not used autonomic blocking agents in these procedures; undoubtedly, as reported by Glenn,[4] they are equally satisfactory. However, in the younger age group, in which category most of our patients belong, it is not unusual to find that autonomic blockade will not induce sufficient hypotension, whereas arteriotomy never fails to do so.

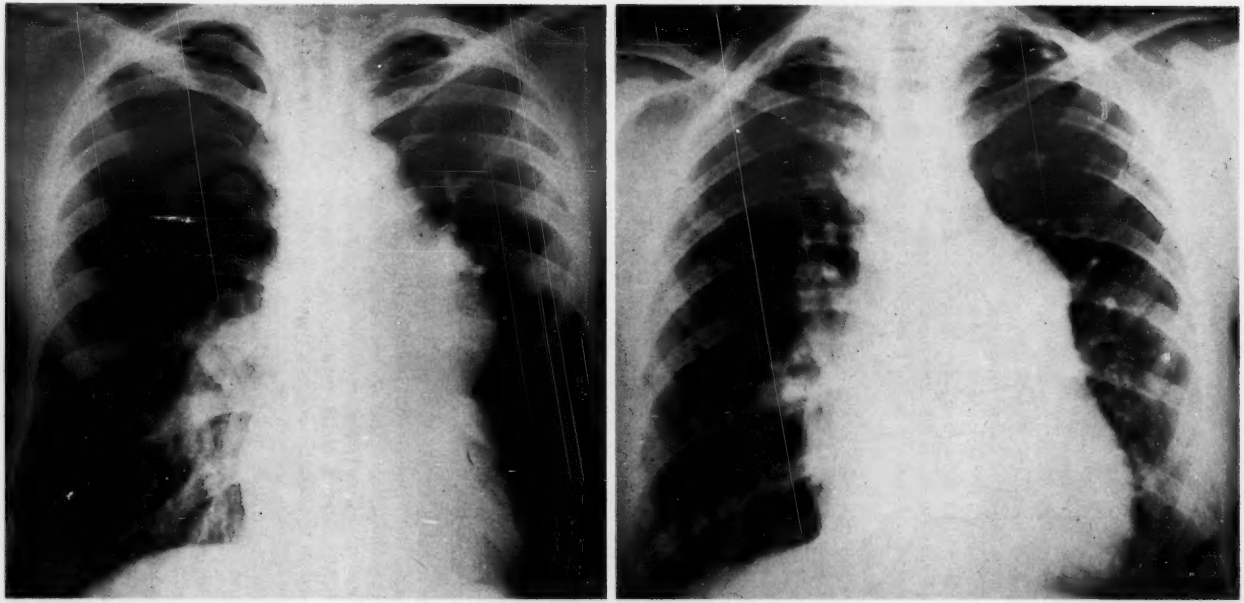
Most cases of complicated patent ductus arteriosus may be foretold from preoperative examination, including radiographic and catheterization studies. Upon inspection of the ductus at the time of surgery, it is usually apparent that it has undergone degenerative changes: the tense, pulsating vessels have a brittle appearance that is formidable to the surgeon who contemplates the operative division. Following the use of controlled arteriotomy bleeding, which allows induction of precise and variable hypotension, it is extremely gratifying to be able to see that the involved vessels have become soft and pliable. With reduction in intraluminal pressure, a significant decrease in vascular caliber occurs.

We believe that every patent ductus arteriosus should be divided. In the complicated case, one has little choice but to divide the ductus, since ligation of a degenerated or window type of ductus is particularly hazardous. When the patient is hypotensive, the ductus can be much more adequately mobilized and clamps can be applied well back onto the softened parent vessels, thus obtaining adequate cuffs for closure even of the very short ductus.

A brief summary of each of the four cases in which this technic was used follows.

CASE REPORTS

Case 1. A 28 year old white woman had a patent ductus arteriosus and aneurysmal dilatation of the pulmonary artery as shown in figure 2. By cardiac catheterization she was found to have pulmonary hypertension and there was decreased oxygen saturation of the blood in the femoral artery as compared with that in the brachial artery, due to partial shunt reversal through the ductus. At operation the ductus measured 2.5 cm. in diameter and there was marked dilatation of the pulmonary artery. The ductus and adjoining pulmonary artery appeared to have undergone degenerative changes and appeared to be very friable. After exposure of the area, controlled hypotension was



a b

Fig. 1. The two roentgenograms demonstrate the degree of aneurysmal enlargement which can occur in response to pulmonary hypertension. (a) The roentgenogram of the chest of the patient in whom the operation terminated in fatal hemorrhage. (b) (Case 1) The roentgenogram of the chest of the patient in whom hypotension was first utilized. Note the generalized increase in pulmonary vascular markings in addition to the aneurysmal enlargement of the pulmonary artery.

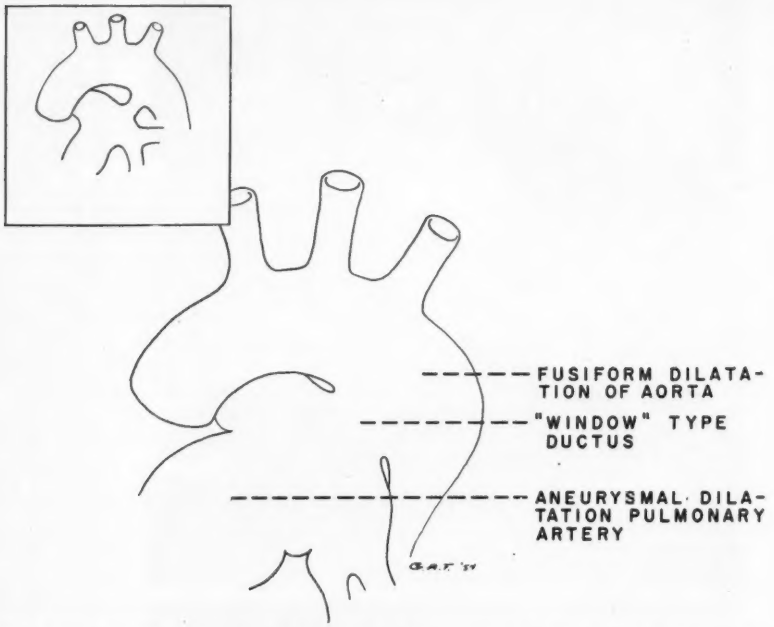


Fig. 2. (Case 1) Diagrammatic representation of the anatomic finding in case 1. Attempting to occlude this type of ductus by ligature obviously would be hazardous. Tying down a ligature about this type of ductus puts undue traction on the parent vessels and is apt to cause a tear. This is in contrast to the usual finding depicted in the inset where ligature or division is relatively simple.

induced. With the removal of 1200 cc. of blood, the pressure was reduced from 100 mm. Hg systolic to 68 mm. Hg. There was no resultant tachycardia and her general condition seemed satisfactory without overt signs of oligemic shock. Considerable softening of the involved vessels was immediately apparent and the pulmonary artery was definitely decreased in size. Mobilization of the ductus was then completed. It was clamped, divided, and closed in the usual manner without difficulty. Following closure of the ductus most of the withdrawn blood was reinfused. At the conclusion of the operative procedure the pressure was stable at 90 mm. Hg systolic. The patient had an uneventful postoperative course.

Case 2. The patient was a 19 year old white woman. Approximately two years previously she had had simple ligation of a patent ductus and within six months there were signs of recanalization. At operation there was marked thickening of the pleura about the great vessels and it was extremely difficult to develop tissue planes in the vicinity of the ductus. The risk of serious hemorrhage seemed greatly increased. Controlled hypotension was induced by withdrawal of 1100 cc. of blood with a fall of systolic pressure from 120 mm. Hg to 70 mm. Hg. There was a prompt softening of the vessels and an apparent increase in pliability. Dissection was then completed without difficulty and the aortic end of the ductus was clamped with a large Potts-Smith type of clamp.

The ductus was divided and the ends were sutured without difficulty. Sufficient blood was reinfused to elevate the systolic pressure to 115 mm. Hg at the close of the procedure, and the patient had an uncomplicated postoperative course.

Case 3. An 18 year old white man was diagnosed as having a large patent ductus. At operation, a window-type ductus, 1.5 cm. in diameter, was encountered. There was some pleural reaction overlying the ductus, and plaques were palpable in its wall. It was also evident that there was increased pressure in the pulmonary artery. For these reasons, the systolic pressure was reduced from 130 mm. Hg to 90 mm. Hg by removal of 400 cc. of blood; subsequently, removal of an additional 250 cc. was necessary to maintain the hypotension. A considerable improvement in the texture and softness of the great vessels resulted, and they were readily mobilized. The ductus was clamped, divided, and the ends were closed without incident. Blood pressure was returned to 110 mm. Hg systolic by reinfusion of blood. The patient had an uneventful postoperative convalescence.

Case 4. A 10 year old white girl was found at operation to have a short ductus, 1 cm. in diameter, with associated fusiform dilatation of the aorta and early aneurysmal changes in the pulmonary artery. During mobilization of the aorta, it was noted that the ductus appeared to have undergone significant degenerative changes. Therefore, 200 cc. of blood was removed from the radial artery causing a fall in blood pressure from 110 mm. Hg systolic to 80 mm. Hg. Subsequently, it was necessary to remove several additional quantities of blood, which totaled 175 cc., to maintain the hypotension between 70 and 80 mm. Hg systolic. Mobilization was then readily completed; however, during the division, the Potts ductus clamp became dislodged from the pulmonary end of the ductus. It proved to be no problem to occlude the opening with Allis clamps and then to suture it. There were no postoperative complications.

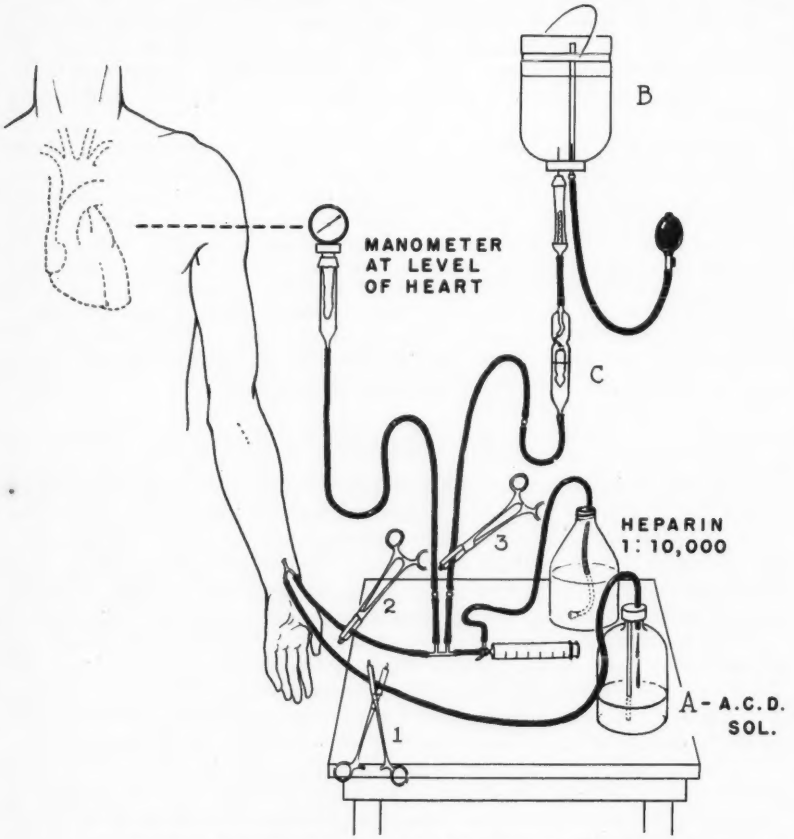
TECHNIC

During operation, hypotension is induced by withdrawal of blood from a radial artery. The cut down and arteriotomy need not be performed until the need for hypotension is ascertained during exposure of the ductus. The necessary equipment is kept in a sterile kit and is immediately available (fig. 3). The blood is collected under aseptic conditions in the usual transfusion bottles containing A.C.D. solution. The blood pressure can be measured directly by an aneroid manometer connected with the system. This permits a continuous check on the blood pressure and additional blood can be withdrawn or reinfused as indicated. Heparin is intermittently infused into the system to prevent clotting. It is important to establish limits of time and degree of hypotension to add to the safety of the procedure. We strive to keep systolic pressure above 70 mm. Hg and to utilize this degree of hypotension for no more than 30 minutes. When the need for hypotension has passed, the appropriate amount of blood to restore a safe blood pressure is reinfused. In each of the cases described above some surplus blood was banked for possible future use.

PHYSIOLOGIC CONSIDERATIONS

Bleeding will not induce hypotension until the discrepancy between the capacity of the vascular system and the blood volume has exceeded the limits

of the various compensatory mechanisms. It is likely that these compensatory mechanisms are depressed by anesthesia so that a drop in blood pressure results from a smaller blood loss in the anesthetized patient. It has been impressive to us that these patients under anesthesia have not developed the marked tachycardia, weak pulse, and sweating, signs ordinarily associated with oligemic shock. It may be thought that arteriotomy induces oligemic shock. Our experience indicates that it does not. Hypotension, if severe and of long duration,



(By permission of SURGERY, GYNECOLOGY AND OBSTETRICS.[3])

Fig. 3. Setup for arteriotomy bleeding. Blood is withdrawn by opening clamp 1. When clamp 2 is opened the arterial blood pressure is continually recorded by the manometer. Clamp 3 is opened only when blood is being reinfused from bottle (B). The MacIntosh drip (C) precludes the possibility of air entering the arterial tree. Heparin is added to the system intermittently to preclude clotting.

may be a precursor of shock, but it is not synonymous with it. Shock is prevented during induced hypotension by careful control of the level of the blood pressure and by limiting the length of time that it is depressed. In our group of patients, maximal hypotension has been utilized for only 15 to 30 minutes and then it is rapidly reversed by reinfusion of blood. Also, 70 to 80 mm. Hg systolic has been set as an arbitrary lower limit for blood pressure. Pressure levels below this limit are counteracted by blood replacement. There have been no detectable changes in any body systems following this procedure. We are unprepared to state whether a typical shock syndrome would ensue if the hypotension was prolonged, but it seems reasonable that it would. The patient in shock from hemorrhage of any source will usually manifest hypotension as the only sign for a significant period early in the development of the syndrome.

SUMMARY AND CONCLUSIONS

Hypotension induced by arteriotomy bleeding during surgery has been used in four cases of complicated patent ductus arteriosus. We believe that this technic is of considerable value in simplifying the operative procedure and in reducing the hazard of uncontrolled blood loss. The use of this technic brings about very significant softening and increase in pliability of the involved blood vessels. There were no postoperative complications of any kind in the four cases in which the technic was utilized. It should be stressed that a time limit of 30 minutes and a low pressure limit of 70 mm. Hg systolic are considered to be important safety factors when the technic is used.

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BELL'S PALSY TREATED WITH CORTISONE

Review of Literature and Report of Cases

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BELL'S palsy was first treated with cortisone in 1951, Rothendler[1] reporting the first case. Cortisone therapy was begun the day after the paralysis appeared; definite improvement in the palsy was noted within three days and complete recovery in seven days. The next year, Robbins[2] reported one case of Bell's palsy in which treatment with cortisone was begun nine days after the onset of the paralysis. Improvement was noted within 24 hours; there was complete recovery in 12 days.

In 1953 Rothendler[3] reported seven more cases. In all instances, therapy with cortisone was begun from one to ten days after the paralysis appeared. In all but one of the cases, within the first week of treatment recovery had begun and by the end of the second week recovery was complete. In the case that did not respond, the paralysis had been present for ten days and atrophy of the nerve had resulted, as indicated by the faradic test.

The report of five cases by Whitty[4] lacks details; however, it states that in four cases cortisone therapy was begun within 48 hours and, in the fifth case, within four days of the onset of paralysis. In three of the five cases improvement was noted within 14 days after treatment had been initiated.

Robinson and Moss[5] reported two cases. In one, treatment with cortisone was started within three days of paralysis; there was definite improvement three days later, and complete recovery in six days. In the other case, the Bell's palsy had been present one week when cortisone was first administered. There was marked improvement by the fifth day of treatment, and by the tenth day there was virtually complete recovery.

In addition to the above cases, there have been two reports of cortisone in the treatment of Bell's palsy that occurred as one manifestation of the Guillain-Barré syndrome. In February 1952, Stillman and Ganong[6] reported the first case treated with ACTH and cortisone. Among the multiple neurologic signs was bilateral Bell's palsy. ACTH was administered one day after the facial paralysis appeared and within 48 hours the paralysis had disappeared except for a slight defect on the right side of the face. After 12 days of treatment with ACTH, slight facial weakness was again noted. Cortisone was substituted for ACTH, resulting in the prompt disappearance of the facial weakness. The second case was reported by Vernon[7] in January 1954. In addition to the other neurologic findings, the patient had a bilateral Bell's palsy that had been present for 12 days. On the third day of treatment with ACTH, the patient

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could whistle, wrinkle the forehead, and close the right eye but not the left eye. After ten days of treatment, cortisone was substituted for ACTH. After five days of cortisone therapy, there was only residual damage to the seventh nerve. The patient was maintained on cortisone, and one month after the initial treatment with ACTH, the cranial nerves were found to be intact.

Since January 1954, eight of our patients with Bell's palsy have been treated with cortisone. In five patients the disease was acute; in three it was chronic. We used the cortisone regimen suggested by Robinson and Moss:[6]

50 mg. three times a day for two days, followed by
50 mg. twice a day for two days, followed by
25 mg. three times a day for ten days.

In three patients, the unilateral Bell's palsy was chronic, having been present for, respectively, 2, 10, and 20 months. The patient in whom the disease had been present for two months was possibly slightly worse after the two weeks of treatment. In the patient whose palsy had been present for ten months, there was only slight improvement; no effect was noted in the patient whose disease had been present for 20 months. These three chronic cases are therapeutic failures.

In the five acute cases, cortisone therapy was started from 2 to 14 days after the Bell's palsy appeared. In four of the five patients there was marked improvement within 11 to 17 days after the beginning of treatment. In the fifth patient in whom the cortisone treatment is considered to have failed, there was slight improvement in that he could blow out his cheeks, and smaller quantities of food lodged in the buccal cavity.

CASE REPORTS

Case 1. The patient was a 36 year old white man who, two weeks before initial examination, had noted aching in the left ear and at the angle of the left mandible. The day following this aching, he had numbness of the left side of the face, and found it difficult to close the left eye; also, there was excess lacrimation and blurred vision in that eye. Physical examination revealed a simple type of Bell's palsy with no involvement of the geniculate ganglion or fallopian canal elements. The Bell's phenomenon was not strongly positive; the palsy was most prominent in the perioral musculature. Cortisone therapy was administered for 14 days; three days after treatment was stopped, the patient no longer experienced difficulty chewing food, he could whistle and blow out his cheeks. The only abnormality noted was an exaggeration of the orbicularis oculizygomaticus complex when he tried to wink the ipsilateral eye.

Case 2. The patient was a 34 year old white man. He had developed a left facial palsy 23 days prior to, and a right facial palsy two days prior to initial examination. The parasympathetic and taste components of the chorda tympani were not involved. Twelve days after the institution of cortisone therapy, the right (recent) Bell's palsy had almost completely disappeared. There was only a faintly positive Bell's phenomenon on the right; the right corneal reflex was very active; and food no longer collected in the right buccal cavity. The left facial paralysis which had been present for 23 days prior to treatment was not affected. He was advised to continue cortisone 25 mg. twice a day for 12 more days. One month after initiation of therapy, there had been only slight improvement on the left side.

Case 3. The patient was a 27 year old white man. One week prior to initial examination he had noted that the left side of his face seemed flat, and taste on the left side of the mouth was abnormal. He was unable to blink the left eye, in which there was excess lacrimation. Examination revealed the Bell's phenomenon, contralateral exaggerated ciliary reflex, inability to furrow the left brow, and typical inability to retract the left angle of the mouth. Eleven days after treatment was begun, almost all of the signs had disappeared. The only residual symptoms were incomplete furrowing of the left brow, and weak retraction of the left angle of the mouth.

Case 4. The patient was a 46 year old white woman. Five days prior to initial examination she had noted pain behind the right ear. The following day she noted that liquids escaped from the right angle of the mouth, and she then realized that the right side of her face was paralyzed. Physical examination revealed a simple type of Bell's palsy. Bell's phenomenon was present. Cortisone therapy was started four days after the onset of the palsy. Within three to four days after the onset of treatment, she began to notice improvement. She was seen again two days after the course of treatment was completed. At that time there remained only a slight weakness of the perioral musculature; she could close her eye, furrow her brow, blow out her cheeks, and food no longer collected in the buccal cavity.

Case 5. The patient was a 31 year old white man. Six days prior to initial examination he had noted sagging of the left side of the face, inability to close the left eye, and collection of food in the left buccal cavity. Four days after the onset of symptoms, cervical sympathetic block, performed elsewhere, had no effect. Twenty-two days after the onset of treatment (eight days after treatment was stopped) he again was seen. There was some subjective and objective improvement. He could blow out his cheeks, and food collected in smaller quantities in the left buccal cavity. The Bell's phenomenon remained prominent. He was advised to continue cortisone 25 mg. three times a day for ten more days. At the end of that time, food no longer collected in the buccal cavity, but the other findings were unchanged.

DISCUSSION

Prior to this report, findings in 16 cases of Bell's palsy treated with cortisone had been published. In all of these cases the Bell's palsy had been present no longer than ten days before the initiation of cortisone treatment. In all but three of these patients, there was either marked improvement or cure within 14 days, which appears to be a considerably shorter time than one could expect in the natural course of the disease. In the two reported cases of Guillain-Barré syndrome with facial palsy that were treated with ACTH and cortisone, the effects of therapy were similar.

SUMMARY

The literature of the treatment of Bell's palsy with cortisone is reviewed. Eight additional cases are discussed: three chronic cases and one acute case did not respond to the treatment; four of the five acute cases demonstrated marked improvement within 11 to 17 days after starting cortisone therapy.

The treatment of acute Bell's palsy with cortisone appears to be of value in accelerating recovery from a simple neurapraxic type of injury to the seventh cranial nerve. Although definite conclusions are not justifiable on the basis of

the small number of cases thus far reported, further study of the cortisone treatment is clearly indicated.

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REPAIR OF THE CLEFT LIP

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ONE out of every eight hundred children in the United States is born with a cleft lip, a cleft palate, or both. Within this group of congenitally deformed infants, 25 per cent will have only a cleft lip, 50 per cent a cleft lip associated with cleft palate, and the remaining 25 per cent a cleft palate alone.[1] The cosmetic deformity of the cleft lip, often mistakenly called "harelip," even today carries with it a social stigma of major proportions. During recent years, improved surgical technics and their widespread use by well-trained plastic surgeons have succeeded in reducing the degree of deformity to the point where in most cases it should not be a serious problem to the patient.

The mechanism by which the defect is produced may be explained as the failure of the median nasal and maxillary processes to fuse during the second fetal month. While objection can be raised to this theory, no more reasonable explanation has been offered. The cause of this noncoalescence remains obscure, though experiments with animals have shown that many congenital anomalies may be reproduced by modifying the chemical environment of an embryo during specific periods of its growth. The concept that inheritance is a major factor in the appearance of the defect is increasingly accepted, since 30 to 40 per cent of these patients present a family history of the same deformity.[1]

It is important to understand that a congenital deformity involving the mouth and face is a problem requiring integrated medical supervision. Not only the services of the surgeon, but those of the pediatrician, the dentist, the otolaryngologist, and the speech therapist will in all probability be essential to proper care of the patient. In some cases the assistance of the psychiatrist may be required. It is not enough for the surgeon to repair a cleft lip or palate and then to divest himself of the responsibility associated with producing a socially adjusted adolescent or adult.

From the surgical standpoint, one attempts to accomplish four specific ends in the repair of a cleft lip. First, the cleft must be closed. Secondly, an effort is made to reconstruct normal cosmetic features, such as nostril symmetry, fullness of the vermilion, a smooth vermilion border and normal eversion of the lower third of the lip. Thirdly, the scar of the repair should be minimal and not deforming. Finally, damage to blood supply and growth centers must be avoided by meticulous planning and careful handling of tissues. It has been shown that surgical damage contributes prominently to the secondary growth difficulties so common in persons with this defect.[2]

Preoperative Management

Much has been published in recent years concerning the proper age at which to repair the cleft lip. While it is obvious that increased size of the in-

volved structures makes possible a slightly more precise operative procedure, it is equally evident that if one carries this theme to its logical conclusion, no congenital defect should be repaired prior to adulthood. The latter course is patently impractical if one considers its social implications. One likewise must recognize the concern of the horror-struck parents of an infant newly born with a deformity of this magnitude. With these factors in mind and with much accumulated evidence that the mortality rate of the surgical procedure remains negligible, we elect to repair the lip as soon as possible after birth. Surgery during this immediate postnatal period is well tolerated by the infant. Jaundice, marked loss of weight, weight less than six pounds, or evidence of other congenital or acquired disease are contraindications to immediate surgery.

In preparing the baby for surgery, a single feeding is withheld if feedings have already been started. No preoperative medication is used. The baby should be securely wrapped at the start of the procedure to avoid his manually contaminating the surgical field. A moderate Trendelenburg position with the operator sitting at the infant's head, is utilized. The anesthetic agent of choice is ether, preferably administered into the pharynx through a soft rubber catheter sutured to the tongue. It is unwise to undertake ether anesthesia with other than an experienced anesthetist in attendance, since it may be difficult to maintain the infant within the narrow limits between dangerously deep anesthesia and anesthesia so light that precise surgical manipulation is impossible. The amount of anesthetic agent required and of incidental loss of blood may be reduced if 1 per cent procaine containing 5 to 10 drops of 1 to 1000 epinephrine per ounce is infiltrated locally following marking of the lip.

Operation

The plan of repair of the cleft lip depends in considerable degree on the type of defect to be closed. Briefly, cleft lips may be classified as complete, single or double, and with or without associated alveolar defect and/or cleft palate.

Two plans are in common use for closure of the single lip, with comparable results. In the first, outlined by Brown and McDowell,[3] a small triangular flap is constructed on the lateral side of the defect, to supply both fullness and eversion of the lower segment of lip and to break the straight line of scar (fig. 1). The second method, originally presented by Hagedorn in 1892 and recently revised by LeMesurier,[4] utilizes a small square or rectangular flap for the same purpose (fig. 2). The surgeon's personal preference will be the significant determining factor in his choice of methods. In the complete cleft lip markedly deficient in soft tissue, the former plan may offer some advantage.

The lip is marked with methylene blue according to either of these plans (figs. 1 and 2). In these figures, ab must equal $a'b'$; bc must equal $b'c'$; and cd must be of the same length as $c'd'$. The points c and c' in figure 1 and d and d' in figure 2 are on the vermilion border at levels where vermilion is sufficiently full to permit adequate repair.

Incisions are made as shown, using thumb and index fingers across the

Fig. 1. Repair of unilateral cleft lip using a small triangular flap at the vermilion border.[3] (A) Plan of incisions. (B) Result following closure.

Fig. 2. Repair of unilateral cleft lip by means of a rectangular flap.[4] (A) Plan of incisions. (B) Result following closure.

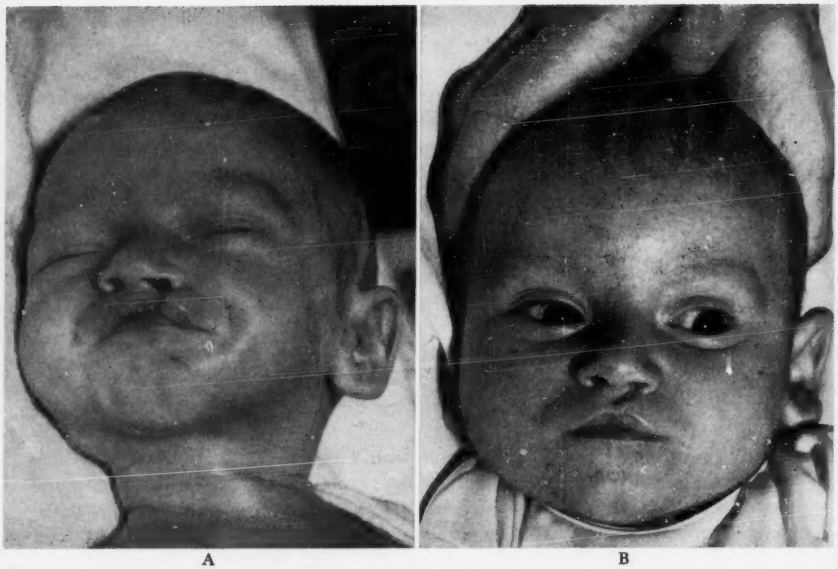
lateral aspect of the lip as an atraumatic clamp to control bleeding. The buccal fornix is incised and the lip freed from the alveolar ridge as necessary. Minimal lateral mobilization by blunt dissection is carried out only if there is insufficient relaxation to permit closure without it. The nasal cartilages are left undisturbed unless there is severe distortion of the superior aspect of the nostril, in which case the overlying skin may be dissected from the cartilage with fine-pointed scissors to permit realignment of these tissues. The vermilion is incised either to interdigitate or to close vertically, depending on the amount of tissue available.

The lip margins are accurately approximated, using two or three 4-0 chromic catgut sutures in the muscle layer, and 7-0 black silk in the skin. Vermilion and all mucosal edges are closed with slightly heavier black silk. A single mattress stay suture is usually placed from the posterior aspect of the lip at the base of the nostril.

No dressing is applied. A small, vaseline-gauze plug in the newly constructed nostril may be useful for 24 hours to prevent swelling if dissection of the cartilage has been carried out. A Logan clamp prevents accidental trauma to the lip following operation.

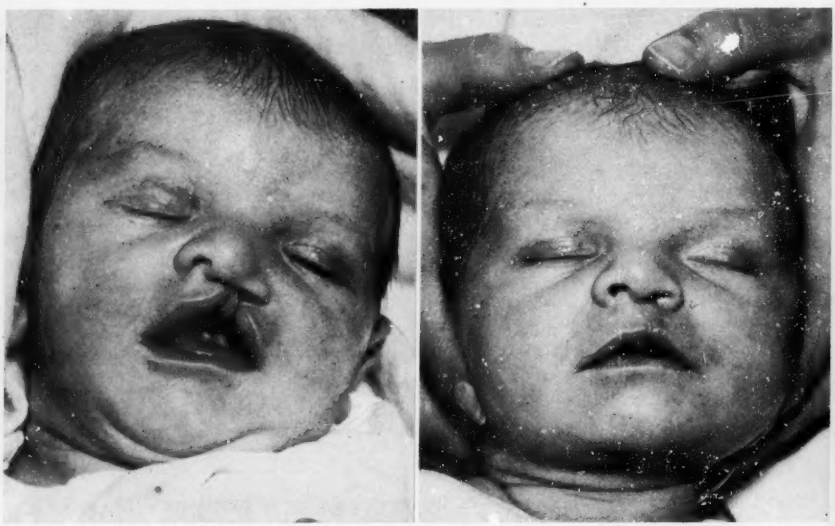
The planning of the repair of a double cleft is similar, though with less satisfactory end results. Either a square or a triangular flap is outlined on each side, depending on the size and shape of the premaxilla and the desired vertical height of the lip (fig. 3). If there is any question as to the proper length, one is advised to err on the side of shortness. Not only is the normal infant lip a short one, but if future revision is to be carried out, the lip can be lengthened with ease, while the reverse procedure of shortening may be difficult and yield unsatisfactory results.

Fig. 3. Repair of bilateral complete cleft lip, showing the use of a rectangular flap on each side of the cleft. The shape and size of the premaxillary tab as well as the desired lip length will determine the type and dimensions of these flaps. (A) Plan of incisions. (B) Result following closure.



A B

Fig. 4. Incomplete unilateral cleft lip. (A) Preoperative. (B) Postoperative.



A B

Fig. 5. Complete unilateral cleft lip. (A) Preoperative. (B) Postoperative.

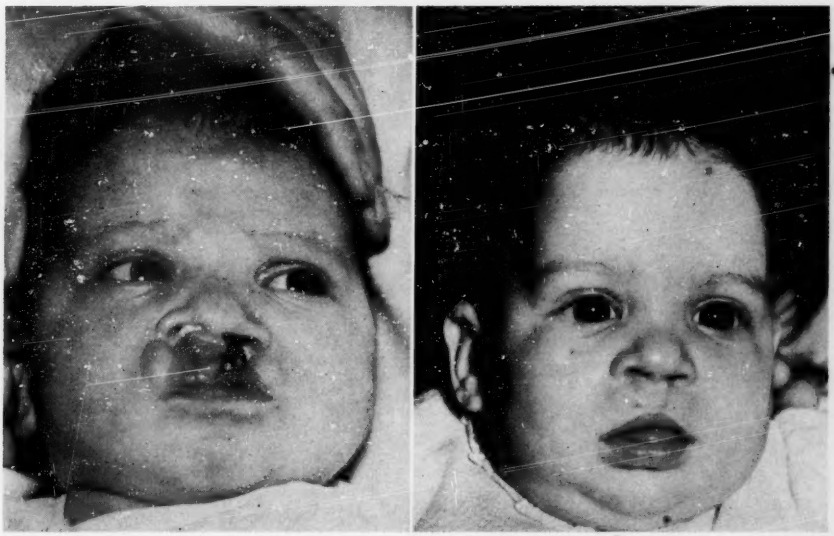
If possible, the lip is closed without manipulation of the bony portion of the premaxilla, even if a two-stage closure is required. Occasionally, the premaxillary tab is so displaced that it must be set back toward the alveolar ridges. This is accomplished by removal of a small wedge of septum, followed by fixation by means of a straight needle passed through the premaxilla into septum and vomer. Lip repair is done at the same time.

Once again, it should be emphasized that minimal tissue damage and minimal disturbance of blood supply and growth centers are essential to the normal development of these facial structures. One cannot urge too strongly the value of precise planning and meticulous technic.

Postoperative Management

The immediate postoperative care is simple and straightforward. The lip is cleansed with saline sponges every hour for the first day and thereafter as necessary, to prevent the formation of crusts around the sutures. Feedings by bulb syringe are started as soon as possible after the infant leaves the operating room. Intravenous fluids are administered only if necessary. Skin and vermilion sutures are removed on the fourth postoperative day; mucosal sutures remain until time of discharge on the ninth or tenth day. When the baby is discharged, a soft nipple may be safely substituted for the feeding syringe.

It is anticipated that the repair of an associated cleft palate will be carried



A B

Fig. 6. Bilateral cleft lip: right side incomplete, left side complete. Repair carried out using a small rectangular flap from each side. (A) Preoperative. (B) Postoperative.

out 15 to 18 months later, if the lip has been repaired at birth. At that time the original lip repair is re-evaluated and a program outlined for additional surgery as necessary to reconstruct the nasal columella or revise the nose or lip. In most instances this can be undertaken before the child reaches school age, but often it cannot be completed until middle or late adolescence. During the waiting period the resources of all the allied specialists will be essential to the normal maturation of the patient.

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THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

announces the Second Annual Postgraduate Continuation Course in Pediatrics for September 29 and 30, 1954.

CURRENT THERAPY IN PEDIATRIC PRACTICE

Tentative Program

Wednesday, September 29, 1954

8:00- 9:00 a.m.	Registration	
	Morning Session	R. D. Mercer, M.D., Presiding
9:00- 9:05 a.m.	Opening Remarks	F. A. LeFevre, M.D.
9:05- 9:15 a.m.	Treatment of Congestive Heart Failure	W. L. Proudfit, M.D.
9:15- 9:25 a.m.	Treatment of Coma	Theodore Mortimer, M.D.*
9:25- 9:35 a.m.	Treatment of Convulsions	E. M. Zucker, M.D.
9:35- 9:45 a.m.	Recognition of Poisoning	Irving Sunshine, M.D.*
9:45- 9:55 a.m.	Treatment of Complications of Steroid Therapy	J. R. Haserick, M.D.
9:55-10:15 a.m.	Intermission	
10:15-10:25 a.m.	Treatment of Tuberculosis	H. S. Van Ordstrand, M.D.
10:25-10:55 a.m.	Diagnosis and Treatment of Adrenogenital Syndrome	Lawson Wilkins, M.D.*
10:55-11:05 a.m.	Roentgenologic Diagnosis of Adrenal Disease	E. F. Poutasse, M.D.
11:05-11:15 a.m.	Respiratory Distress in the Newborn	Viola Startzman, M.D.
11:15-11:25 a.m.	Treatment of Stridor	Samuel Spector, M.D.*
11:25-12:00 a.m.	Questions and Answers	
12:00- 1:30 p.m.	Luncheon—Courtesy Bunts Institute	
	Afternoon Session	Viola Startzman, M.D., Presiding
1:30- 1:40 p.m.	Treatment of Purpura	J. S. Hewlett, M.D.
1:40- 1:50 p.m.	Treatment of Acquired and Congenital Hemolytic Anemias	J. D. Battle, Jr., M.D.
1:50- 2:00 p.m.	Treatment of Sickle Cell Anemia	John Harris, M.D.*
2:00- 2:10 p.m.	Treatment of Secondary Anemia	C. Q. McClelland, M.D.*
2:10- 2:20 p.m.	New Roentgen Diagnostic Technics	A. S. Tucker, M.D.
2:20- 2:30 p.m.	Procedures in Evaluation of Intelligence	Miss Clare Robinson
2:30- 2:45 p.m.	Intermission	
2:45- 3:30 p.m.	Panel Discussion—Constitutional Variations in Adolescence	Lawson Wilkins, M.D.* E. P. McCullagh, M.D. Samuel Spector, M.D.*
3:30- 3:50 p.m.	The Year in Pediatrics	R. D. Mercer, M.D.
3:50- 4:30 p.m.	Question and Answer Period	

Thursday, September 30, 1954

	Morning Session	Viola Startzman, M.D., Presiding
9:00- 9:10 a.m.	Hyperthyroidism	R. S. Dinsmore, M.D.
9:10- 9:20 a.m.	Surgery of Thyroglossal Duct Anomalies	George Crile, Jr., M.D.

9:20- 9:30 a.m.	Maxillofacial Tumors in Children	H. E. Harris, M.D.
9:30- 9:40 a.m.	Recognition of Brain Tumors	W. J. Gardner, M.D.
9:40- 9:50 a.m.	Cardiac Arrest	C. E. Wasmuth, M.D.
9:50-10:10 a.m.	Intermission	
10:10-10:20 a.m.	Dysplasia of the Hip	R. D. Mercer, M.D.
10:20-10:35 a.m.	Fulminating Ulcerative Colitis	R. B. Turnbull, Jr., M.D.
10:35-11:20 a.m.	Abdominal Neoplasms in Infants and Children	R. M. Wansbrough, M.D.*
11:20-12:00 a.m.	Questions and Answers	
12:00- 1:30 p.m.	Luncheon—Courtesy Bunts Institute	
	Afternoon Session	R. D. Mercer, M.D., Presiding
1:30- 1:40 p.m.	Treatment of Esophageal Stenosis	L. K. Groves, M.D.
1:40- 1:50 p.m.	Treatment of Diaphragmatic Anomalies	D. B. Effler, M.D.
1:50- 2:10 p.m.	Treatment of Small Intestinal Obstructions in Infants	E. W. Gerrish, M.D.*
2:10- 2:25 p.m.	Surgery of the Biliary Tract in Children	S. O. Hoerr, M.D.
2:25- 2:35 p.m.	Surgical Treatment of Burns	Robin Anderson, M.D.
2:35- 2:45 p.m.	Trauma of the Eye	R. J. Kennedy, M.D.
2:45- 2:55 p.m.	Bone Tumors of Children	A. W. Humphries, M.D.
2:55- 3:05 p.m.	Roentgen Therapy of Malignancy	R. A. Hays, M.D.
3:05- 3:15 p.m.	Intermission	
3:15- 4:00 p.m.	Panel Discussion—Preoperative and Postoperative Care of Children	R. M. Wansbrough, M.D.* D. E. Hale, M.D. Viola Startzman, M.D. Robin Anderson, M.D.
4:00- 4:30 p.m.	Question and Answer Period	

* Guest Speaker

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Please register me for the course on "Current Therapy in Pediatric Practice" to be given September 29 and 30, 1954. (Registration Fee is $15.00, except for interns and residents, and members of the Armed Forces in uniform, who will be admitted free.)

I am enclosing check for $5.00 and the remainder will be paid on registration September 29.

Checks should be made payable to the Frank E. Bunts Educational Institute.

Name .....

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This course is open only to graduates of approved medical schools.

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

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DISEASES OF THE CHEST

October 27 and 28, 1954

Sponsored by

CLEVELAND SOCIETY FOR DISEASES OF THE CHEST

and

AMERICAN COLLEGE OF CHEST PHYSICIANS

Tentative Program

Wednesday, October 27, 1954

8:00- 9:00 a.m. . Registration

Morning Session . . . . . H. S. VAN ORDSTRAND, M.D., Presiding

9:00- 9:05 a.m. . Opening Remarks . . . . . F. A. LEFEVRE, M.D.

9:05- 9:25 a.m. . Present Status of Antimicrobial Treatment . . HAROLD CURTIS, M.D.*

9:25- 9:45 a.m. . Pathology as Affected by Antimicrobial Therapy . . . . . THOMAS KINNEY, M.D.*

9:45-10:05 a.m. . Surgical Trends in Tuberculosis . . . HARVEY MENDELSOHN, M.D.*

10:05-10:25 a.m. . Immunization with BCG . . . . . M. M. PERLICH, M.D.*

10:25-10:45 a.m. . Trends in Tuberculosis Control . . . . . J. B. STOCKLEN, M.D.*

10:45-11:00 a.m. . Intermission

11:00-11:30 a.m. . Diagnosis and Antibiotic Therapy of the Pneumonias . . . . . THEODORE WOODWARD, M.D.*

11:30-11:50 a.m. . Mucoviscidosis . . . . . R. D. MERCER, M.D.

11:50-12:10 p.m. . Diagnostic Value of Kveim Test in Sarcoidosis . J. R. HASERICK, M.D.

12:30- 2:00 p.m. . Luncheon—Courtesy Bunts Institute

Afternoon Session

2:00- 3:30 p.m. . Panel Discussion—

Emphysema . . . . . H. S. VAN ORDSTRAND, M.D., Moderator
GEORGE WRIGHT, M.D.*
R. N. WESTCOTT, M.D.
DAVID GILLESPIE, M.D.*

3:30- 3:45 p.m. . Intermission

3:45- 5:00 p.m. . Panel Discussion—

Pneumoconiosis . . . . . RAYMOND MCKAY, M.D., Moderator*
SIDNEY WOLPAW, M.D.*
H. S. VAN ORDSTRAND, M.D.
GEORGE WRIGHT, M.D.*

Thursday, October 28, 1954

Morning Session . . . . . F. A. LeFevre, M.D., Presiding

9:00- 9:20 a.m.	Surgery of Septal Defects	Earl B. Kay, M.D.*
9:20- 9:40 a.m.	Surgery of Congenital Heart Disease	D. B. Effler, M.D.
9:40-10:00 a.m.	The Experimental and Clinical Use of the Heart-Lung Apparatus	George Clowes, M.D.*
10:00-10:20 a.m.	Pericardial Biopsy	W. L. Proudfit, M.D.
10:20-10:40 a.m.	Cardiac Arrest	C. E. Wasmuth, M.D.
10:40-11:00 a.m.	Intermission	
11:00-12:00 noon	Panel Discussion— Surgery in Mitral Stenosis	A. C. Ernstene, M.D., Moderator F. M. Sones, Jr., M.D. Salvatore Sancetta, M.D.* Henry Zimmerman, M.D.*
12:30- 2:00 p.m.	Luncheon—Courtesy Bunts Institute	
	Afternoon Session	D. B. Effler, M.D., Presiding
2:00- 2:15 p.m.	Cytologic Studies in Lung Cancer	L. J. McCormack, M.D.
2:15- 2:45 p.m.	Diagnosis and Treatment of Bronchogenic Carcinoma	Walker Munz, M.D.*
2:45- 3:15 p.m.	Management of Mediastinal Tumors	Fred Cross, M.D.*
3:15- 3:30 p.m.	Intermission	
3:30- 3:50 p.m.	Coin Lesions	L. K. Groves, M.D.
3:50- 4:20 p.m.	Lung Biopsy in Diffuse Lung Lesions	H. S. Van Ordstrand, M.D.
4:20- 4:45 p.m.	Middle Lobe Syndrome	D. B. Effler, M.D.

* Guest Speaker.

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Please register me for the course on "Diseases of the Chest" to be given October 27 and 28, 1954. (Registration Fee is $15.00, except for interns and residents, and members of the Armed Forces in uniform, who will be admitted free.)

I am enclosing check for $5.00 and the remainder will be paid on registration, October 27.

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Medical School and
Date of Graduation.....

This course is open only to graduates of approved medical schools.

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

A detailed program of the postgraduate course, "Review Course in General Surgery," that is scheduled for November 17 and 18, 1954, will appear in the October issue of the QUARTERLY.

Basic Science Course

The Basic Science Course in Medicine will start on Saturday, September 18, 1954. The Course consists of two lectures weekly and during the fall term will cover the field of endocrinology.

A Review Course in Surgery will begin its weekly sessions on Wednesday, September 22, 1954.

SURGICAL TREATMENT OF ARTERIOSCLEROSIS OBLITERANS

A Preliminary Report

ALFRED W. HUMPHRIES, M.D.
Department of Orthopedic Surgery

FAY A. LeFEVRE, M.D. and VICTOR G. deWOLFE, M.D.
Department of Cardiovascular Disease

ENCOURAGING results have been noted in the majority of patients who during the past six months have received surgical treatment for arteriosclerosis obliterans of the aorta, the iliac, or the femoral arteries. The disease has been treated by resection of the occluded segment and establishment of continuity of the vessel with a frozen-dried arterial graft. In 12 of the 14 patients receiving the surgical treatment, the postoperative courses have so far been favorable.

Arteriosclerosis obliterans may be diffuse or segmental in nature. It tends to be diffuse in patients 60 years of age or older; whereas the segmental form usually occurs in patients 40 to 50 years of age in whom the arteries are otherwise mildly involved. Our preliminary report is limited to cases of the segmental form, since only this type is amenable to the surgical procedure of grafting.

In the segmental form of the disease, the presenting complaint is intermittent claudication of the back, buttock, hip, thigh, or calf, the location depending upon the vessel occluded. The principal finding is the absence of pulses below the point of occlusion in an otherwise essentially normal limb.

Angiographic visualization of the anatomic pattern reveals the details of the occlusion, which determine operability. A typical example of angiographic visualization is shown in figure 1: the occlusion is at the aortic bifurcation, extending approximately 2½ inches down the common iliac artery. The other vessels appear to be normal. Figure 2 shows the resected specimen, the graft used, the operative procedure, and the postoperative aortogram.

The salient features of the surgical procedure are:

Continuous spinal anesthesia offers the best control of the patient during operation.

To keep the graft open, adequate head pressure and volume flow must be provided during the operation and the immediately postoperative period by the maintenance of blood pressure at levels over 100 systolic and of pulse rate at 70 or above. As the diameter of the grafted vessel decreases, it becomes increasingly important to maintain the blood pressure and pulse rate at the specified levels.

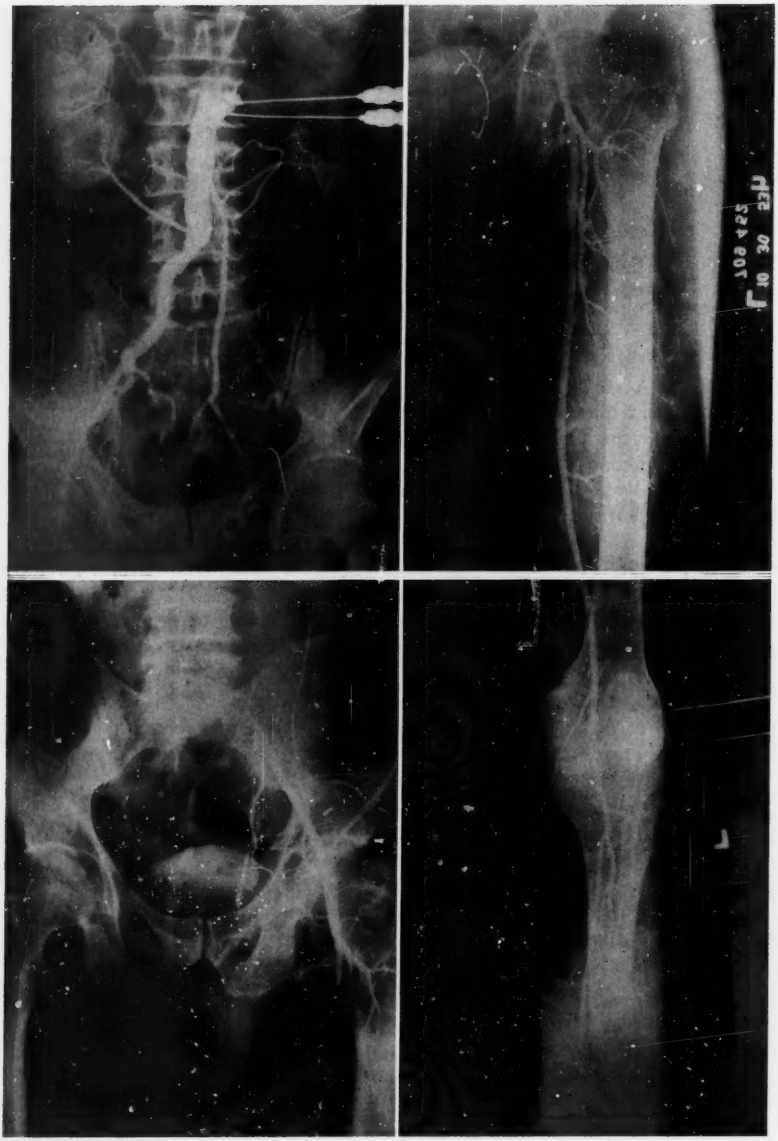

Fig. 1. Aortogram, retrograde arteriogram, and continuate arteriogram, showing block left common iliac artery.

Free flow of blood distal to the graft is essential. Obstruction of the flow can be determined preoperatively by continuate arteriography (fig. 1); and at surgery, after resection of the occluded segment, presence of free flow is evidenced by a forceful retrograde flow from the distal vessel.

To prevent embolization of operative soft clots, three safeguards are employed: (1) adequate washing of the lumina of the isolated vessels; (2) irrigation of the vessel to be anastomosed, by permitting a free flow of blood both in direct and in retrograde directions just prior to the closing of the anastomosis with the last two or three sutures; and (3) injection of 10 mg. of heparin into each isolated vessel at the time it is clamped off.

Intimectomy of the distal vessel is not advisable since the rough edge may be loosened from the wall by the flow of blood, fall across and block the lumen, or break free as an embolus. It may be necessary to do a proximal intimectomy in high aortic blocks.

Calcification of the host aortic bifurcation usually necessitates the use of a bifurcate graft in cases of unilateral common iliac artery occlusion. In these cases it is preferable to establish circulation to the unobstructed limb first, since it has not been protected by the development of collaterals.

Preservation of all possible collaterals is desirable, but frequently it is necessary to sacrifice those collaterals immediately above and below the occluded segment in order to anastomose the graft to a part of the vessel that is reasonably patent.

The inferior mesenteric artery may be transected, apparently without danger to the lower bowel; this is an important consideration, since this vessel frequently must be sacrificed in grafts to the aorta.

The preoperative and postoperative findings in our first 14 cases are reported in the table.

COMMENT

In 9 (cases 6—14) of the 14 patients, the results of operation are satisfactory at this time both to patient and to examiner. In three (cases 1, 2, and 4), although the symptoms of the presenting complaints have been appreciably relieved and the patient is satisfied with his condition, the blood supply has not been fully restored to the limb. In one of these three (case 4), exploration of the posterior tibial artery at the time of grafting revealed the artery to be occluded by old atheromata. In that case, and presumably in the other two, the lack of full restoration of blood supply is due to blocks distal to the graft. As has been stated above, free flow of blood distal to the graft is essential.

Case 5 was unusual in that when the patient was admitted the left leg was pregangrenous. Angiographic study showed occlusion of the left common iliac artery and both of its branches, and occlusion of the superficial femoral artery. The entire visualized supply of blood to the left leg was from the deep femoral artery which, in turn, was supplied only by collaterals derived from the aorta itself. The right common iliac artery had a large filling defect that did not

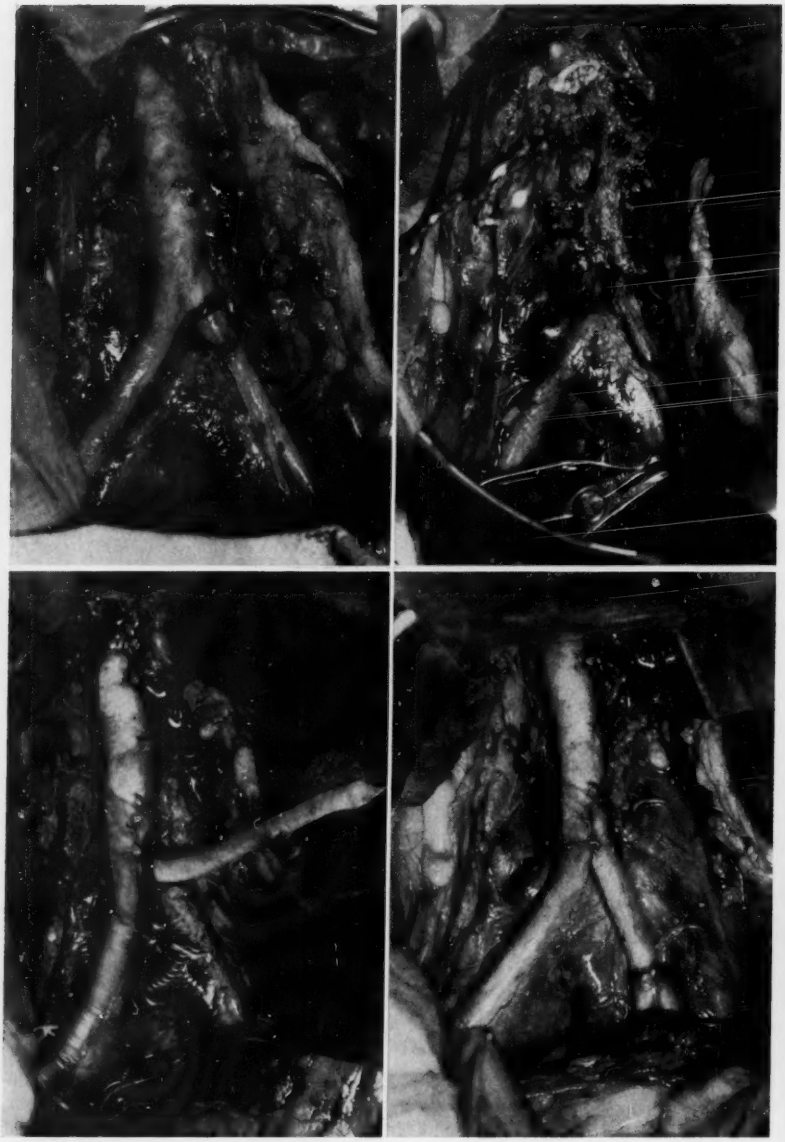

Fig. 2A. Operative procedure showing the exposed diseased artery, the aortic bed following resection, the right limb of the graft in place, and the entire graft in place.

Fig. 2C. Frozen-dried aortic bifurcate graft.

Fig. 2B. Resected specimen showing complete occlusion right iliac ostium.

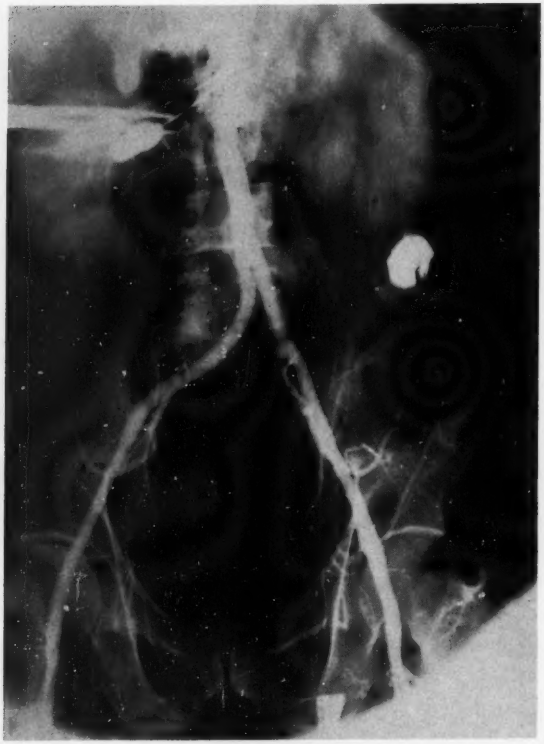

Fig. 2D. Immediate postoperative aortogram. The apparent narrowing at the anastomosis lines represents operative spasm in the host vessel and becomes mechanically dilated during the next few days.

completely occlude the lumen. At operation, the graft was placed from the aorta to the lower common iliac artery on the right, and to the common femoral artery just proximal to the deep femoral artery on the left. This was done to protect the right leg and with the hope that an improved head of pressure might save the left leg. The left leg improved for several weeks, after which time it reverted to its preoperative condition. Aortography at that time revealed that the right limb was patent, but the left limb of the graft was occluded at the bifurcation. This also is an example of partial failure of a graft due to the absence of a free flow of blood distal to it.

The other unsatisfactory result, case 3, occurred in a patient who died on the fifth postoperative day of renal failure following prolonged occlusion of the aorta proximal to the renal arteries.

TABLE
Preoperative and Postoperative Findings in 14 Patients Grafted for

TABLE

Preoperative and Postoperative Findings in 14 Patients Grafted for Arteriosclerosis Obliterans

Case no.	Age (yr.)	Walking distance before pain occurred; other complaints Preop.	Postop.	Sites grafted	PULSES Femoral Preop.	Femoral Postop.	Popliteal Preop.	Popliteal Postop.	P.T. Preop.	P.T. Postop.	D.P. Preop.	D.P. Postop.	Time Postop.	Remarks
1	51	Less than ½ block	2 blocks	C.F.	+	+++	0	0	0	0	0	0	6 mo.	
2	62	1 block	4 blocks	C.I.	0	+	0	0	0	0	0	0	6 mo.	
3	57	½ block	—	A.B.	0	—	0	—	0	—	0	—	5 days	Died; renal failure.
4	64	1 block	4 blocks	F.	++	++	0	0	0	0	0	0	3 mo.	Despite absent pulses, walking distance markedly increased.
5	61	Rest pain, left leg	Unchanged	A.B.	L 0 R +++	0 ++++	0 ++	0 +++	0 +++	0 ++	0 0	0 ++	1 mo.	See Comment, p. 199.
6	56	2 blocks	Unlimited	F.B.	0	++++	0	+++	0	+++	0	+++	4 mo.	
7	62	1 block	Unlimited	A.B.	L 0 R ++	++++ ++++	0 ++	++ +++	0 ++	+ +++	0 ++	0 +++	5 mo.	
8	48	½ block	Unlimited	A.B.	L ++ R 0	++++ ++++	0 0	++++ ++++	0 0	++++ ++++	0 0	++++ ++++	5 mo.	
9	65	1 block; night pain	Unlimited this leg	F.	L +++	+++	0	+++	0	+	0	+++	4 mo.	Untreated block present, right leg.
10	46	1 block	Unlimited	F.	+++	+++	0	+++	0	+++	0	0	3 mo.	
11	41	1 block	Unlimited	A.B.	L 0 R++++	++++ ++++	0 ++++	++++ ++++	0 ++	+++ ++	0 ++++	++++ ++++	2 mo.	
12	49	1 block	Unlimited	A.B.	L 0 R 0	++++ ++++	0 0	++++ ++++	0 0	++++ ++++	0 0	++++ ++++	2 mo.	Patient had had a prior resection of aortic bifurcation.
13	49	50 feet	Unlimited	A.B.	L 0 R +	++++ ++++	0 0	++++ ++++	0 0	++++ ++++	0 0	++++ ++++	1 mo.	
14	57	½ block	Unlimited	A.B.	L 0 R 0	+++ ++++	0 0	+++ ++++	0 0	+ +	0 0	+++ ++++	1 mo.	

Abbreviations used: C.F. —common femoral
C.I. —common iliac
A.B. —aortic bifurcation
F.B. —femoral bifurcation
F. —femoral

SUMMARY

In the segmental form of arteriosclerosis obliterans, angiographic visualization of the occlusion determines whether surgical treatment can be used. Resection of the occluded segment and establishment of continuity of the vessel with frozen-dried arterial graft has proved satisfactory in 12 of 14 patients so treated. The salient features of the surgical procedure are outlined.

CANCER OF THE STOMACH

STANLEY O. HOERR, M.D.
Department of General Surgery

CANCER of the stomach is regarded by some physicians as the equivalent of a death warrant. This view is fostered by the infrequency of cured cases in the experience of any single physician, as well as by some published reports that stress the pessimistic aspects of the disease. No such implication attaches to cancer of the breast; yet, if the patient with cancer of the breast has fixation of the tumor to the chest wall, or distant metastases to bone, no mastectomy is carried out and, in most series, the patient does not figure in the five-year survival statistics. Not so with cancer of the stomach; most studies scrupulously include every instance of the diagnosis, whether or not the patient ever is examined by a surgeon, and whether or not the diagnosis is confirmed by histologic study of tissue removed from the tumor or one of its metastases.

In studies of cancer of the stomach, we should distinguish between the different stages of the disease at the time treatment is carried out. It is not at all unusual to read that five-year survivors comprise 25 to 30 per cent of all patients with gastric cancer in whom a gastric resection "for cure" has been carried out (i.e., all gross evidence of tumor has been eradicated). The percentages are not very different from those for five-year survivals reported for radical mastectomy for cancer of the breast, and at the time of surgery the two conditions are comparable: as far as the surgeon can tell, the cancer has been entirely removed. The condition of a patient who has a gastric carcinoma that is irresectable because of fixation to the aorta, for example, is analogous to that of a patient with cancer of the breast which is irresectable by reason of extension to the chest wall. The fact that clinical examination can establish inoperability in the case of the breast lesion, whereas an abdominal operation is required to establish inoperability in the case of the gastric lesion, does not alter the basic similarity. Until a hopeless situation is disclosed by operation, we should adopt the same attitude of cautious optimism which we entertain toward "operable" cancer of the breast.

Differentiating the stage of the disease at the time of operation is of practical importance. Without it, we excuse ourselves for lack of an aggressive attitude toward treatment of the patient whose lesion may be malignant but is probably benign, on the grounds that if the lesion is not cancer, no urgency for surgical treatment exists; and if the lesion is cancer, the outlook is hopeless anyway. What are the facts to support a modest optimism in "operable" (i.e., potentially curable) cancer of the stomach?

Practical Import of a Clinical Classification of Cancer of the Stomach. The writer recently has proposed[1] a clinical classification of cancer of the stomach based upon two aspects of the disease: (1) the presence or the absence

of *metastases*, and their surgical accessibility if present; (2) the degree of *invasion* by the primary tumor.

In regard to point 1, three possible stages of *metastases* are designated as follows:

Stage A—*No metastases.*

Stage B—*Regional metastases.* These usually are resectable and hence are consistent with a potential cure.

Stage C—*Distant metastases.* These include metastases to liver, lung, supraclavicular lymph nodes, peritoneum, and bone. At the present time they mean incurability.

In regard to point 2, three possible stages of *invasion* by the primary tumor are designated as follows:

Stage I—*Superficial cancer*, confined to the inner layers of the gastric wall. Bulky or extensive cancers are not excluded, but all may be resected.

Stage II—*Cancer in all gastric layers.* As in Stage I, cancers may be extensive or bulky, but all are resectable, since neighboring structures are not invaded.

Stage III—*Extragastric invasion by the cancer.* The tumor has extended to one or more organs outside the stomach, such as colon, mesocolon, liver, pancreas, or aorta. Resectability depends upon the resectability of the organ or that part of it which the tumor has invaded.

Every cancer of the stomach may be classified by a combination of two symbols: A, B, or C designating the stage of metastases, and I, II, or III designating degree of invasion. A stage A-I lesion is a superficial cancer without evidence of any metastases, regional or distant. The outlook should be excellent. A stage C-III lesion is one that has distant metastases and invasion of neighboring structures by the primary tumor. The outlook is hopeless. Lesions in stages C-I, C-II, and C-III all are incurable, because all have distant metastases; whether or not the stomach is resected has no bearing on the prognosis. (A special case of hopeless lesions with distant metastases is designated as stage C-NX, meaning that the degree of invasion by the primary tumor is unknown. An example is the condition in the patient who has the clinical history and roentgenographic findings consistent with gastric carcinoma, where biopsy of a supraclavicular lymph node establishes the existence of distant metastases, but on whom no laparotomy is performed.)

All stage A-I and stage A-II lesions are resectable and potentially curable (no metastases, and the primary tumor either superficial or confined to all coats of the stomach). Nearly all stage B-I and stage B-II lesions are resectable and potentially curable (regional metastases, and primary tumor either superficial or confined to all gastric layers); the only exceptions to potential curability will occur when the regional nodes themselves are not resectable. On the other hand, potential curability of stage A-III and stage B-III lesions (involvement of organs outside the stomach by extension of the primary tumor, and either no metastases, or regional metastases) depends entirely on the dispensability of the structures that have been invaded by the primary tumor.

The correlation of this clinical classification with the actual results of surgery in patients has been tested on a personal series of 100 consecutive patients having primary operations for carcinoma of the stomach, each followed either to a fatal termination of the illness or for periods ranging from 18 months to 4 years. The results, summarized in the table, show that so far, in this admittedly short follow-up, the classification has practical utility in predicting the outcome. All seven patients with stage A-I lesions are living without evidence of disease, whereas all 34 patients in stage C (C-II, C-III, C-NX) are dead of their disease.

A practical use of the classification is given in figure 1, where patients are divided into two comprehensive groups: those with potentially curable lesions as determined at operation, and those with clinically incurable lesions. The relation between the clinical stage and survival without disease in this limited follow-up is clearly shown.

Can the Clinical Stage of Cancer of the Stomach be Determined Without Operation? A surgical procedure usually will be necessary to establish the stage of the disease, as well as to furnish histopathologic proof of its exact nature. This surgical procedure will not always be a laparotomy. Examples where a tissue diagnosis may be obtained without a laparotomy include the following: biopsy of an involved supraclavicular node; biopsy of a bony metastasis; needle biopsy of an hepatic metastasis or of a metastatic mass in the pouch of Douglas (Blumer's shelf); demonstration of malignant cells in ascitic fluid. In each instance it is assumed that there is clinical and roentgenographic evidence of a gastric neoplasm. All such cases are classified as Stage C-NX (distant metastases but no knowledge of the degree of invasion of the primary tumor).

It may be asked why, in the examples just given, a clinical diagnosis will not suffice, avoiding the expense and inconvenience to the patient of any surgical procedure. There are two reasons for obtaining a tissue diagnosis even when the disease seems to be hopelessly advanced: firstly, there is always the possibility of an error in the clinical appraisal and, secondly, tissue diagnosis may disclose a lesion that could be treated advantageously with roentgen therapy or nitrogen mustard, for example, reticulum cell sarcoma, Hodgkin's granuloma or lymphoma or lymphosarcoma. In connection with clinical errors, the writer has seen an "involved" stony-hard supraclavicular node prove to be a cervical rib (this patient is now living and apparently free from disease three years after a total gastric resection); hepatic "metastases" have been cirrhosis of the liver; "ascites" has been adipose tissue; a "Blumer's shelf" has been an incarcerated, retroverted uterus. These errors, ridiculous as they may seem in retrospect, were made by experienced clinicians, and if these misdiagnoses had been used as the basis for advising treatment, they might have prevented an operation for a potentially curable lesion.

If it is sometimes difficult to be certain of the existence of distant metastases without an operation, it is impossible, without an operation, to determine the degree of invasion of the primary tumor or the presence or absence of regional metastases. In particular, the roentgenographic appearance of a gastric neoplasm is not a reliable means of determining resectability of the local lesion.

TABLE
Results of Primary Operations for
Carcinoma of the Stomach in 100 Patients
(Minimum Follow-up—18 Months)

Stage of carcinoma	No. of patients	Resection for cure	NUMBER OF PATIENTS			
			Hospital death	Dead of disease	Living with disease	Living without disease
A-I	7	7	0	0	0	7
A-II	15*	14	2	6	1	6
A-III	12	9	0	7	0	5
B-I	1	1	0	0	0	1
B-II	12	12	0	6	1	5
B-III	19	11	2	16**	0	1
C-I	0	—	—	—	—	—
C-II	7	0	1	6	0	0
C-III	20	0	1	19	0	0
C-NX	7	0	0	7	0	0
TOTAL	100	54	6	67	2	25

** Stomach not resected in one patient when operation was discontinued because of poorly taken anesthetic; patient subsequently died in the hospital.*
*** One patient died after secondary operation for stricture of esophageal anastomosis.*

One patient died after secondary operation for stricture of esophageal anastomosis.

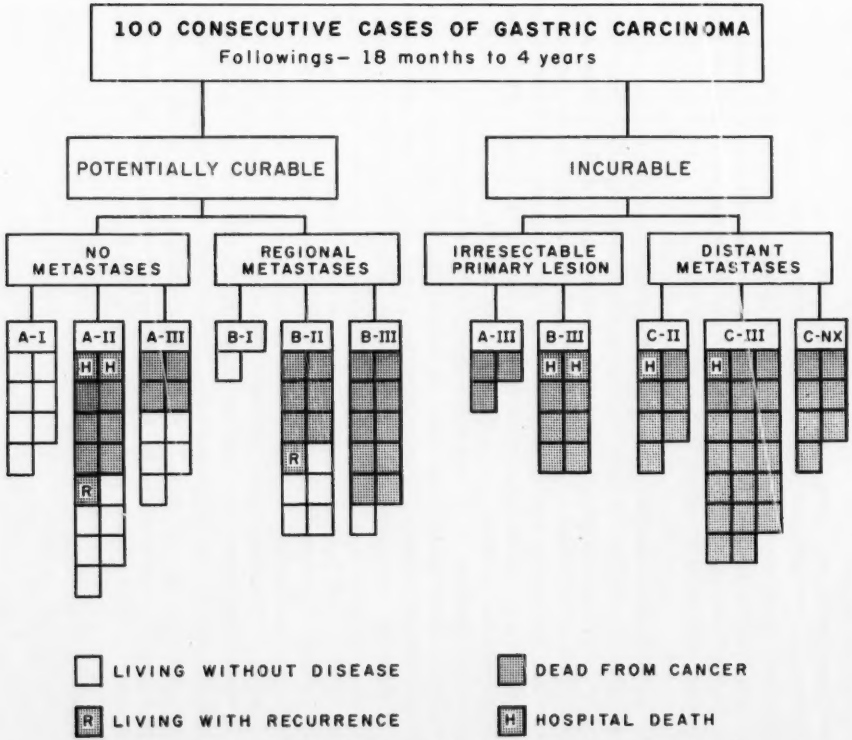

Fig. 1. Chart showing relation between clinical stage and survival without disease.

An unfavorable-appearing lesion, from a roentgenographic standpoint, high in the fundus of the stomach in a man of nearly 80 years, which was threatening his life by hemorrhage, proved to be a well-localized leiomyosarcoma, easily and adequately treated by a local excision without gastric resection. Even tumors that involve the entire stomach, as viewed by the radiologist, may be easily resectable because there is no extension beyond the stomach. The duration of symptoms, the appearance of the lesion through a gastroscope, the presence or absence of a palpable abdominal mass, all are unreliable criteria of the potential curability or incurability of a given lesion.

One may conclude that if the patient physically is able to undergo an operation, he is entitled to a laparotomy to determine whether the lesion is resectable and potentially curable, and if not curable by surgery, whether it is a histopathologic type amenable to roentgen therapy.

Is the Operative Fatality Rate Prohibitive? Because of the nature of the disease, and the debility of many of the patients who require surgery, the operative mortality rate from operations for gastric cancer always will be substantially greater than that of operations for benign conditions such as duodenal ulcer, where the fatality rate as given by many surgeons is 1 per cent or less. In the author's series brought up to date there were 12 operative fatalities (about 8 per cent) in 145 patients undergoing primary laparotomy for gastric malignancy. Fortunately, the operative mortality rate seems to be lower in the more favorable lesions. There were six deaths in a total of 82 resections for potentially curable lesions, making a mortality rate of slightly more than 7 per cent. There were five deaths in a total of 15 palliative resections or short-circuiting procedures, a mortality rate of 30 per cent. (There was one death in 48 patients who underwent simple exploration with biopsy.) Although this latter percentage is unduly high (two deaths were sudden and were not directly related either to the disease or to the type of operation), it is consistent with the experience of others that palliative procedures are appreciably more hazardous than curative resections, no matter how radical. It has influenced the author to limit the indications for consideration of palliative surgery.

The six deaths of patients with potentially curable lesions include those of two patients who underwent a total gastrectomy, one patient who had a simultaneous colectomy and gastrectomy for a lesion that involved the colon, one patient whose lesion invaded the liver, one 79 year old patient in whom the operation was discontinued because of a poorly taken anesthetic after partial mobilization of the stomach, and only one patient who had a simple subtotal gastrectomy for a favorable lesion. The mortality rate in simple subtotal gastrectomy for favorable lesions is less than 5 per cent, and cannot be regarded as a legitimate reason for urging patients to avoid operation for a lethal disease.

Is There an Excessive Morbidity Following Radical Operations? Several years ago there was considerable agitation within the profession urging total gastrectomy for every patient with gastric cancer in an effort to improve the over-all results. The illogic of this stand was appreciated by the majority of

surgeons from the very beginning, since recurrence of cancer solely in the remaining stomach is unusual after an experienced surgeon has performed an apparently adequate subtotal gastrectomy. The added risk to life and, equally important, the severe nutritional disturbances that so many patients experience for a good many months afterwards, likewise are cogent arguments against a routine total gastrectomy. Our current practice is to perform a total gastrectomy only when it is required to obtain lines of resection free from disease. We lay much emphasis, on the other hand, upon radical excision of *neighboring* structures that may be involved by continuity, and on a radical removal of regional nodes insofar as this is possible without unnecessary sacrifice of the stomach. Such complicated en bloc dissections increase the operative risk and immediate morbidity, but do not yield the late side-effects of total gastrectomy. A total gastrectomy is required only about once in every five resections for potentially curable lesions (15 of 82 resections in the author's series), and hence late morbidity from ultraradical surgery is kept at a minimum.

Does the Histopathologic Type of Malignant Growth Have an Influence on Prognosis? In a recent study by Fisher and Hoerr[2] the gastric lesions of 100 patients were classified according to four histologic types. The order of apparently increasing malignancy was adenocarcinoma, medullary carcinoma, carcinoma simplex, and scirrhous carcinoma. In mixtures of the various types, behavior was that of the most malignant element present. Scirrhous carcinoma carried a particularly ominous prognosis: none of 21 patients whose lesions contained scirrhous elements was apparently cured of the disease. All of the other histologic types had some apparent cures. Mucinous and colloid variants seemed to be of subordinate importance to the basic types mentioned.

SUMMARY AND CONCLUSIONS

1. Cancer of the stomach essentially is no more hopeless than other forms of malignant disease occurring in more accessible portions of the body.

2. A clinical classification of gastric carcinoma based on the presence or absence of *metastases* and the degree of *invasion* by the primary tumor may assist in a better understanding of the disease by clarifying the potential curability at the time of operation, and the probable outlook for survival.

3. A surgical operation, usually a laparotomy, is necessary in nearly every case to establish the clinical stage of the disease and hence its potential curability. A tissue diagnosis is desirable in every instance to verify the nature of the disease, and to bring to light tumors that might be radiosensitive.

4. Bedside estimates of the presence or absence of distant metastases, or of the resectability of the primary lesion, are subject to grave error even by the most experienced clinicians.

5. The mortality rate is lowest when the procedure is a simple laparotomy and biopsy, and highest when a palliative resection or short-circuiting procedure is carried out. The fatality rate for 145 patients undergoing primary operations

for gastric malignancy was 8 per cent; it was 7 per cent for 82 patients who had resections for potentially curable lesions.

6. Ultraradical operations are reserved for patients whose lesions require it. About one in every five resections for potentially curable lesions is a total gastrectomy.

7. The histopathologic type of the gastric malignancy is of subordinate importance to other features of the disease such as metastases or extension of the primary growth, except for scirrhous carcinoma. There were no cures in 21 patients in this series whose tumors were composed of scirrhous carcinoma in whole or in part.

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WHIPPLE'S DISEASE: REPORT OF CASE APPARENTLY CURED AND DISCUSSION OF THE HISTOCHEMICAL FEATURES

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INTESTINAL lipodystrophy, first described by Whipple,[1] is a rare disorder, the clinical manifestations of which are less well defined than are the pathologic features. Review articles[2,3,4,5] indicate that the onset of the disease is insidious, marked by periodic polyarthritis or arthralgia and, at times, chills and fever. Bowel symptoms vary and, although diarrhea usually appears at some time during the course of the disease, it often is not a prominent complaint or may not occur until late; frequently, constipation may be present. Loss of weight, weakness, fatigability, and general debility are common manifestations. Physical findings may include pigmentation of exposed areas of skin, hypotension, evidence of loss of weight and, frequently, peripheral lymphadenopathy. A palpable, abdominal mass may be present, and there may be a small amount of ascitic fluid. Laboratory examination of the blood frequently reveals a hypochromic or a microcytic anemia and a normal leukocyte count. The roentgenographic findings are not pathognomonic, although disturbances of intestinal motility and alteration of the usual mucosal pattern of the small intestine are not uncommon.

Because of these clinical and laboratory manifestations, differentiation from the sprue syndrome, Addison's disease, or rheumatoid arthritis is often difficult; in fact, few examples of a correct antemortem diagnosis of Whipple's disease are recorded.

Histologically, the lesions of the disease are characteristic. They consist of a marked infiltration of the lamina propria of the small intestine by histiocytes that frequently line cystic spaces of varying size. Although these latter are sudanophilic, the histiocytes fail to stain with Sudan dyes. Their cytoplasms react strongly to the periodic acid-Schiff stain. Occasionally, multinucleated giant cells of the foreign-body type are present within the infiltrated mucosal zone. Similar histiocytic infiltration and varying degrees of fibrosis obliterate the usual architecture of the mesenteric lymph nodes. In addition, evidence of serositis may be present in the capsule of the liver and the spleen. Chylous obstruction has not been present in those instances in which the cisterna chyli and its tributaries have been examined.

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During the past four years, we have observed a patient in whom the diagnosis of Whipple's disease had been made after excision biopsy of a mesenteric lymph node. The results of the histochemical investigation of the excised tissues and the satisfactory clinical course following roentgen and nitrogen-mustard therapy are of particular interest.

CASE REPORT

Clinical Findings

A 27 year old white housewife was examined on July 14, 1950, because of primary complaints referable to a recurrent, migratory polyarthritis and arthralgia that had occurred during the preceding two years. On previous occasions, her symptoms had been diagnosed elsewhere as the result of rheumatic fever and rheumatoid arthritis. She herself had noted having intermittent enlargement and tenderness of lymph nodes (particularly in the cervical chain), recurrent bilateral pleuritic pain, sporadic febrile elevations associated with chills or chilly sensations, fatigue, and weakness. Gastrointestinal symptoms had been sporadic and included vague postprandial epigastric distress, pyrosis, nausea, and occasional vomiting. She had lost 17 pounds in weight during the previous year. The past history was not otherwise significant except that, at the age of 17 years, she had had what her physician referred to as a "butterfly rash" over the nose and malar areas.

The patient was thin and pale. The temperature was 99 degrees F., and the blood pressure was 100/60 mm. Hg. Patches of light-brownish pigmentation were noted on the left forearm and in the left temporal area, and there was slight hyperpigmentation at the borders of the malar erythema. The mucous membranes were pale, and there were discretely enlarged and tender lymph nodes in the cervical chains and in the left supraclavicular area. Findings from the examination of the heart and the lungs were normal, except for the presence of a grade II systolic murmur at the cardiac apex. The remainder of the physical examination revealed no clinically significant findings.

Laboratory studies showed the hemoglobin value to be 8.0 Gm./100 ml.; the blood count to be 3,630,000 erythrocytes and 7600 leukocytes per cu. mm.; and the erythrocyte sedimentation rate 0.87 mm./min. (corrected reading by the Rourke-Ernstene method). Subsequent laboratory studies included: urinalyses; Wassermann and Kahn reactions; blood sugar, cholesterol, urea and urea-clearance determinations; all febrile agglutination tests; cultures of urine, blood, and bone marrow; plasma lupus erythematosus test; serum determinations for calcium, phosphorus, sodium, potassium, and chloride; and routine stool examination; all of which were with normal limits. The examination of the bone marrow revealed hyperplasia of the myeloid series, but there were no diagnostically significant changes. There were no significant abnormalities in the plasma-protein fractions, as determined by electrophoresis.

Roentgenographic examinations of the chest, the gallbladder, the esophagus, the stomach, the duodenum, and the colon, and an intravenous urogram were normal. Interval roentgenographic studies of the small intestines demonstrated that barium had reached the colon at the end of four hours. The barium tended to adhere to the mucosa and there was definite fragmentation and segmentation of the barium pattern.

The frequency and severity of febrile elevations increased. Eventually, the temperature reached 102 to 103 degrees F. daily; the pattern included normal temperatures in the forenoon, with spiked elevations in the afternoon or evening. Therapeutic trials

on penicillin and aureomycin did not alter the clinical picture. The patient's unfavorable clinical course continued until October 20, 1950, approximately three months after initial examination, at which time administration of cortisone was begun and there immediately followed a dramatic subsidence of fever and symptoms. She was afebrile and asymptomatic for six weeks, during which time steroid therapy gradually was withdrawn. There was then a correspondingly gradual return of the clinical signs and symptoms previously described. On January 11, 1951, approximately six months after initial examination, an enlarged lymph node was removed from the left posterior cervical area.

Microscopic Examination

Lymph Node. Sections of this node stained with hematoxylin and eosin revealed preservation of the usual architecture of the lymph node. However, the centers of many of the lymph follicles were occupied by epithelioid cells and an occasional multinucleated giant cell of the foreign-body type (fig. 1). Caseation necrosis was not present. Although

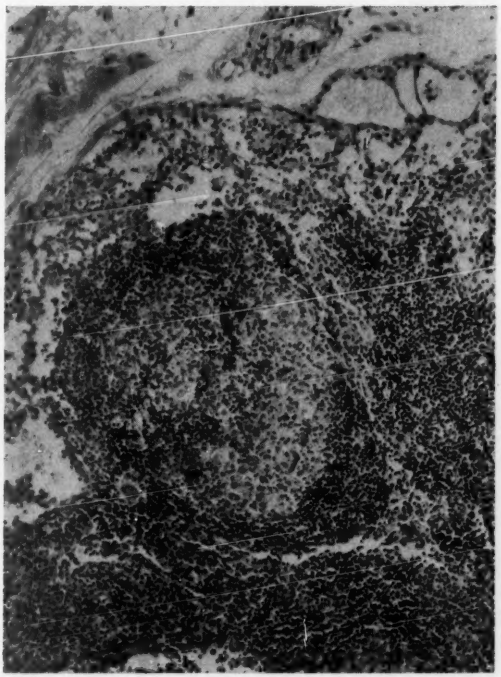

Fig. 1. Section from peripheral portion of cervical lymph node demonstrating ephithelioid reaction. Hematoxylin and eosin. X 90.

the cytoplasms of the epithelioid cells reacted faintly with the periodic acid-Schiff stain, the intensity of this reaction was obviously less than that noted in the histiocytes of the mesenteric lymph nodes subsequently removed, and was similar to that observed by one of us (E.R.F.) as occurring in epithelioid cells in other pathologic states.

About six weeks after removal of the lymph node, a mass was palpated in the left upper abdominal quadrant, and a week later an exploratory laparotomy was performed. In the mesentery of the jejunum, there were a number of very firm lymph nodes measuring 3 to 4 cm. in diameter. The liver was covered with mottled, pale, pinkish-white areas and there were multiple perisplenic adhesions, the result of serosal involvement.

Mesenteric Lymph Nodes. Sections of the mesenteric lymph nodes stained with hematoxylin and eosin revealed obliteration of the usual lymph-node architecture except for the persistence of portions of the peripheral sinus. This alteration was due to the presence of numerous histiocytes having abundant finely granular cytoplasm and round-to-ovoid vesicular nuclei. These cells were arranged in aggregates in addition to lining cystic spaces of varying size, which appeared in paraffin sections to be optically clear (fig. 2). Fibrosis and an inflammatory infiltrate comprised of plasma cells, occasional

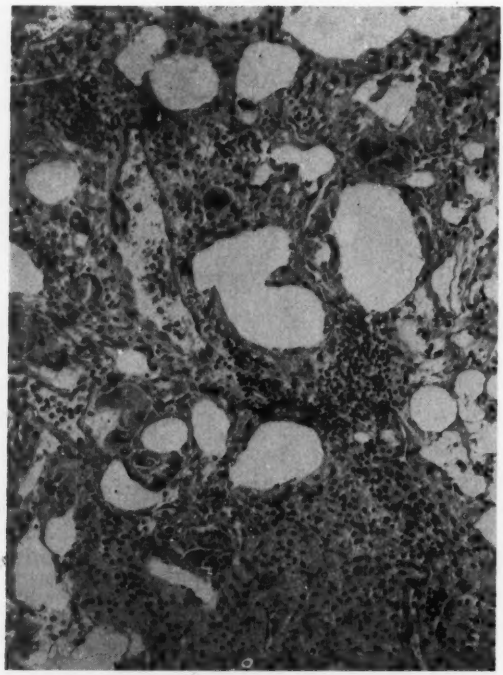

Fig. 2. Section from mesenteric lymph node stained by hematoxylin and eosin. Large cystic spaces are present with aggregates of histiocytes as well as lymphocytic infiltration and an occasional multinucleated giant cell. X 120.

neutrophils and lymphocytes that were arranged in a nodular manner, as well as foreign-body giant cells, were conspicuous within the intercystic tissue. The capsule of the lymph node was markedly thickened and appeared to be comprised of an inner zone of dense, relatively acellular, connective tissue; and an outer zone of more loosely arranged fibrous tissue with areas of fibroblastic and capillary proliferation and numerous histiocytes and giant cells as noted in the main substance of the nodule. The results of the histochemical reactions, performed on the mesenteric lymph node, with reference to the reactions in the histiocytes and cystic spaces are presented in the table.

Liver. A section of liver revealed an increase in the amount of connective tissue of the capsule, with fibroblastic proliferation and lymphocytic infiltration. Fibrin masses were also apparent on the capsular surface. The liver cells contained small cytoplasmic vacuoles that stained with Sudan IV. In addition, moderate glycogen deposition was present within the hepatic cells, as evidenced by the comparison of diastase-digested and diastase-undigested sections stained by the periodic acid-Schiff procedure.

Subsequent to the surgery, roentgenologic therapy to the abdomen was administered. The patient improved, but continued to have intermittent fever to 100 degrees F. and frequent, cramping, abdominal pain. Four months after the roentgen therapy, she was given a course of four intravenously administered doses of nitrogen mustard.

The patient was last examined on June 2, 1954, approximately four years after initial examination, at which time she had no complaints. She had obtained full-time employment and was working regularly in addition to doing her household tasks. There had been rare and short-lived recurrences of arthralgia involving the ankles, with no elevation of temperature. Her appetite was excellent and she had gained 25 pounds since her initial examination, and 40 pounds since hospitalization in October of 1950. There were no abnormal physical findings; the temperature was 99.6 degrees F. (rectally) and the blood pressure 130/78 mm. Hg. She had received no medication since administration of the nitrogen mustard. Laboratory observations demonstrated a hemoglobin content of 13.4 Gm./100 ml.; a blood count of 4,960,000 erythrocytes and 4050 leukocytes per cu. mm.; and a sedimentation rate of 0.45 mm./min. A routine urinalysis was normal.

COMMENT

The pathogenesis of Whipple's disease has not been established. Although early investigators interpreted the pathologic changes as being the result of a primary lipodystrophy, recent studies have suggested the possibility that the changes may be related to an abnormality of ground substance. Inclusion of this disease in the group of so-called collagen diseases has been suggested, and some aspects of the present case support this contention. The subsidence of symptoms following cortisone therapy with recurrence following withdrawal of this substance, as well as the presence of a facial lesion similar to that observed in lupus erythematosus indicate a relationship to the collagen diseases. The combined symptoms of chills and fever, lymphadenopathy and blood alterations suggest generalized systemic involvement.

Upton[6] observed an epithelioid reaction within axillary and other extra-abdominal lymph nodes as well as within the endocardium. In our case a sarcoid-like reaction was also noted within the cervical lymph node removed prior to laparotomy. However, in Upton's and in our cases the results of the

histochemical reactions noted within these histiocytes, and the nonspecific morphologic picture present, indicate that biopsies of peripheral lymph nodes cannot be utilized to establish the diagnosis of this disease.

From the histochemical reactions it becomes evident that the material within the histiocytes that reacts positively to the periodic acid-Schiff stain represents mucopolysaccharide. Since we have been unable to demonstrate a protein or lipid moiety, it is most unlikely that the periodic acid-Schiff reaction is due to glycolipid or glycoprotein as proposed by Black-Schaffer[7] and Upton.[6] The absence of metachromasia within the cytoplasm of these cells indicates that the material is neutral mucopolysaccharide. Although Upton[6] reported positive metachromatic reactions in these cells, our results in failing to elicit metachromasia conform to those noted by Christie and Galton[8] as well as by Casselman.[9]

TABLE

Nature of the Reactions in the Histiocytes and Cystic Spaces of the Mesenteric Lymph Node

(The methods performed are those utilized by Lillie[10] except where indicated.)

METHODS	RESULTS	
	Cystic Spaces	Histiocytes
Sudan Black B, Sudan IV and oil red O (frozen sections)	Positive*	Rarely positive
Sudan Black B on paraffin sections at 25° and 60° C.	Negative	Negative
Periodic acid-Schiff method	Negative	Positive**
Diastase digestion followed by periodic acid-Schiff	—	No change
Hyaluronidase (Wyeth) 1500 TRU/mg. 150/U/cc. in 5.5 sodium acetate-acetic acid buffer for 1 hr. at 37° C. followed by periodic acid-Schiff and Rinehart–Abul-Haj methods	—	No change
Thionine (pH4, 1:10,000) for ½ hour (frozen and paraffin sections)	Negative	No metachromasia
Rinehart–Abul-Haj method	Negative	Positive
Schultz method for cholesterol and esters	Positive	Negative
Fischler's method for fatty acids and soaps	Positive	Negative
Feulgen plasmal for acetal phosphatids	Negative	Negative
Peracetic acid-Schiff reaction for unsaturated compounds	Negative	Negative
Millon reaction for tyrosine-containing protein[11]	Negative	Negative
Diazonium coupling reaction	Negative	Negative
Ferric ferricyanide reduction test	Negative	Negative
Polarization	Positive for birefringent crystals	Negative

* *See figure 3.*
** *See figure 4.*

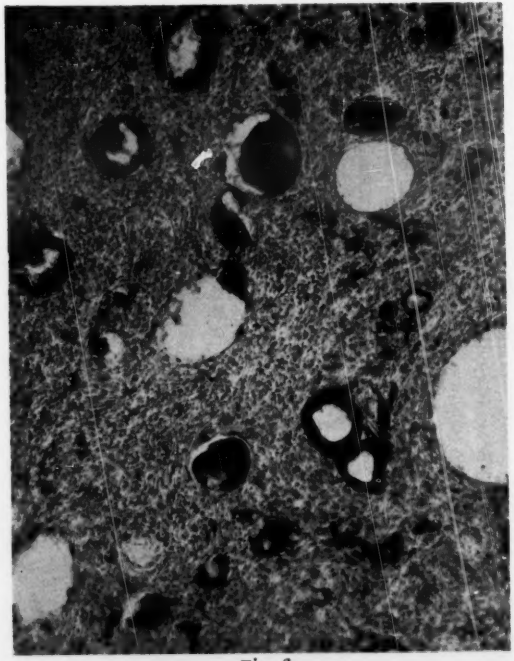

Fig. 3

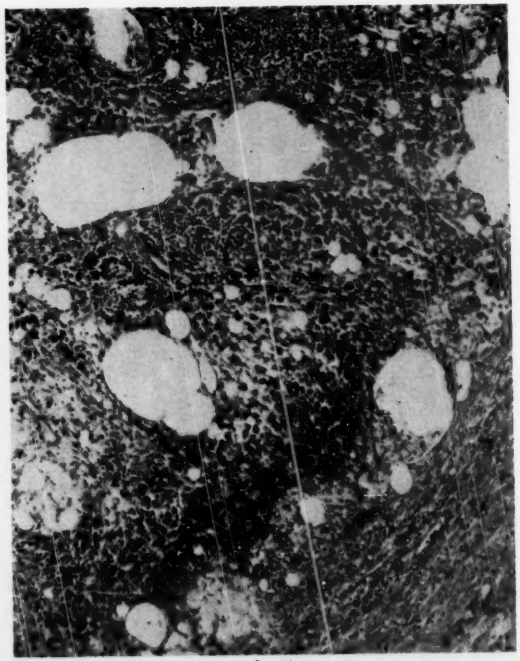

Fig. 4

Fig. 3. Section from mesenteric lymph node stained with Sudan IV. The cystic spaces are positively stained (appear black). X 90.

Fig. 4. Section from mesenteric lymph node stained by the periodic acid-Schiff method The cytoplasms of the histiocytes are intensely colored (appear black). X 90.

Whether the differences observed in the metachromasia represent significant variations in the mucopolysaccharide complex encountered in this disease awaits further investigations.

The occurrence of neutral fats, free fatty acids, soaps, cholesterol and its esters, as well as phospholipids and unsaturated lipids within the cystic spaces has been reported. We have confirmed the presence of these lipids except for the latter two. The question of whether this difference in findings is of the same significance as that noted in the carbohydrate substances observed within the histiocytes, similarly cannot be answered at this time.

The histochemical observations do not elucidate the fundamental derangement responsible for this disease. However, altered lipid metabolism does not appear to be as significant in the etiology of the disease as alterations in mucopolysaccharide: The latter is consistently found in the ubiquitous histiocytes observed in this disease. The possible source for mucopolysaccharide, as Upton[6] has suggested, may be degenerated ground substance, phagocytized epithelial mucin or the reflection of elevated blood hexosamine levels. Although histochemically the carbohydrate substance differs from epithelial mucin, in this case and those reported by Cassellman[9] and Christie and Galton,[8] lacking metachromasia, the possibility of alteration of epithelial mucin cannot be overlooked. Similarly, although the nature of ground substance has not been specifically defined from a histochemical standpoint, at least in some instances such material has been digested from tissue sections by hyaluronidase. This phenomenon did not occur in our case. Yet, alteration of this material either before phagocytosis or following such action could explain the failure of this reaction. Whether such periodic acid-Schiff reactive substance reflects the presence of elevated hexosamine values awaits the determination of this substance in the blood of patients suffering from Whipple's disease.

Although the histochemical studies do not elucidate the pathogenesis of this disease, they are of diagnostic value. According to Hendrix and his associates,[2] certain cases, although considered on cursory examination to be examples of Whipple's disease, on careful scrutiny do not present the characteristics of this disease entity but, instead, are variously examples of chylous obstruction, exogenous lipogranulomatosis, or tabes mesenterica. The marked staining reaction observed with the periodic acid-Schiff in the cytoplasm of the histiocytes is unlike that noted by one of us (E.R.F.) in two examples of chylous obstruction.

The apparently favorable response to irradiation and roentgen and nitrogen-mustard therapy suggests consideration of the application of this type of therapy in other cases of Whipple's disease.

SUMMARY

A case of Whipple's disease, or so-called "intestinal lipodystrophy," is presented in which a satisfactory clinical response has been noted following

roentgen and nitrogen-mustard therapy. The patient has been free of symptoms for four years following diagnosis, and a recent follow-up physical examination and laboratory studies did not reveal any abnormalities.

The histochemical study of the excised mesenteric lymph nodes reaffirms the mucopolysaccharide nature of the cytoplasmic granules observed within the histiocytes found in lesions of this disease. Although the clinical features in this case suggest the possibility that this malady represents a variant of the collagen diseases, the histochemical studies fail to establish such a relationship or the true nature of the disease. However, the histochemical results suggest the need for further biochemical investigation of carbohydrate substances in patients with the disease. The diagnostic significance of the periodic acid-Schiff reaction is emphasized.

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SURGICAL CORRECTION OF VAGINAL RELAXATION

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SELECTION of patients for any operative procedure must be done with the utmost care. In patients having vaginal relaxations, other than those of marked degree, the indications for vaginal plastic must be particularly painstakingly evaluated. Surgical treatment is for the most part elective and should be done only if definite benefits can be offered to the patient.

The term "vaginal relaxation," as used in this paper, designates the lesions resulting from loss of fascial and muscular support of the anterior and posterior vaginal walls. The most important etiologic factor in the development of those conditions is childbirth trauma with the resultant stretching and laceration of fascial and muscular structures. As a consequence of childbirth trauma, in the anterior vaginal wall the pubo-vesicocervical fascia, the urogenital diaphragm and pubococcygeus muscles are most commonly damaged. In the posterior wall, the prerectal fascia, levator muscles and perineal body bear the brunt of the stresses of childbirth.

Factors contributing to vaginal relaxation include all actions that tend to increase intra-abdominal pressure. Among these are lifting of heavy objects, chronic constipation with forced defecation, and chronic coughing or sneezing. Obesity increases the stress on vaginal musculature; menopausal atrophy of supporting structures also is a contributing factor.

Symptoms

Any degree of pelvic relaxation can exist without causing symptoms. Often, the gradual loss of support allows the patient quite unconsciously to adjust to changing sensations. In perception of discomfort, numerous environmental factors play a major role, such as the patient's personality and marital adjustment.

The lesions do not produce pain, though in advanced stages they may result in discomfort that consists of a definite feeling of loss of support. The sensation often is described by patients as a feeling that "the bottom is falling out," or as a "dragging sensation." Patients sometimes loosely speak of back pain but, on careful questioning, they describe it as the sensation of dragging. When back pain per se exists, it is an incidental symptom; it is extremely unlikely that loss of pelvic support will result in true back pain.

Cystocele and so-called urethrocele (a loss of urethral support) may produce various urinary symptoms. Incomplete emptying of the bladder, secondary to loss of support and tone, frequently results in recurrent urinary-tract infections.

Chronic urethritis, however, should not be overlooked as a common source of these infections. Large cystoceles may require digital replacement by the patient in order to be able to initiate micturition.

Stress incontinence results from loss of urethral support with the result that the stresses from coughing, laughing, and sneezing often precipitate uncontrolled loss of urine. It is of considerable clinical importance to differentiate between *stress* incontinence and *urge* incontinence. Urge incontinence is characterized by an inability to retain urine when the desire to void is present, and it generally indicates presence of a lesion within the urethra or bladder. On the other hand, stress incontinence is not associated with a desire to void and occurs with increased intra-abdominal pressure.

Affections of the posterior vaginal wall include lacerations, rectoceles, and enteroceles. Lacerations of less than third degree are asymptomatic. Rectoceles may interfere with normal rectal dynamics by causing feces to be pocketed during the process of defecation. A marked rectocele may have to be pressed upon in order that defecation may take place. It is important to differentiate between symptoms attributable to rectocele and those secondary to constipation.

An enterocele, a herniation of the pouch of Douglas through the posterior fornix, is an uncommon lesion, and when small it may be overlooked. When marked, this hernia may protrude from the vagina. Symptoms caused by it are almost wholly those of simple loss of support.

The condition of the woman who complains that unsatisfactory sexual relations have resulted from loss of vaginal support should be particularly carefully evaluated. The pathologic condition may indeed be the cause of the complaint, but often the difficulty is more amenable to psychotherapy than to surgical intervention.

Examination

Profound relaxation presents little diagnostic difficulty; it is the less obvious relaxation that easily may be overlooked in examination, which may be a diagnostic problem. The examination of patients in lithotomy position makes relaxations, in general, less apparent. Requesting a patient to bear down may overcome this problem. However, the request may not result in the desired increase in intra-abdominal pressure due to fear of embarrassment on the part of the patient over possible passage of flatus or of urine. Traction exerted on the cervix by means of a tenaculum forceps occasionally helps the patient to bear down and may also reveal an otherwise unsuspected prolapse. The cervix is insensitive and accordingly this is not a painful procedure. If symptoms suggest vaginal relaxation, an examination also may be made of the patient in the upright position.

Panendoscopy which includes examination of the bladder and urethra is a valuable routine procedure, as often it will reveal unsuspected pathologic conditions within the urethra or bladder, such as urethral strictures, pathologic conditions of the bladder neck, polypi, or early carcinomas. Thus, needless or unwise operations can be avoided.

Selection of Patients

Patients having pronounced symptoms of vaginal relaxation generally are very desirous of relief. Any or all of the symptoms mentioned above may constitute indication for surgical treatment; however, symptoms and physical findings should complement each other and be of about equal degree. Symptoms out of proportion to relaxation should be suspect as far as vaginal plastic therapy is concerned.

Surgeons should make an effort to evaluate the socio-economic impact of an operation, for if the physician insists on an elective operation, he may relieve symptoms in the pelvis, only to create new symptoms that will arise from the psychic sphere. It may be wise for the specialist to see the patient several times in an attempt to evaluate her personality better. Fortunate, indeed, is the specialist who has the advantage of close liaison with the patient's family physician and can benefit from his personal knowledge of her problems. Most surgeons have seen technically brilliant operative results too often marred by the subsequent development of true pelvic conversion neuroses.

When surgery is being considered, a pessary may serve to indicate to the patient and to her physician just what symptomatic relief can be expected from the operation. Permanent use of a pessary should be reserved for the poor-risk or aged woman, since results generally are not so satisfactory as those of a well-executed operation.

Repairs should not be performed in a patient who has no symptoms, nor should repairs be performed simply because the loss of support seems likely to become more marked with the passage of time. The decision as to the need for operation in the symptomatic patient generally can be left to the patient herself, although the physician, of course, will play a very significant role in directing her to a choice of treatment. The details of findings at examination, and their implications, should be discussed thoroughly with her. She should be guided toward development of a proper perspective in regard to the symptoms and their importance in terms of future good health and the results to be expected from surgery. We as physicians should be careful not to discourage a patient unduly in regard to operation, so that she deprives herself of the benefits that might accrue from relief of real symptoms.

Operative Procedures

Operative technics are well described in most of the standard textbooks of operative gynecology.[1-3] In considering which operation to use, age and physical condition of the patient are of primary concern. In a premenopausal woman the desirability of childbearing and/or menstrual function should be discussed with the patient. Certainly, where there is any possibility of ablating coital function, it should be discussed with the woman, no matter what her age or marital status. Where operative risk is great, as mentioned before, the value of a pessary should not be overlooked. When a pessary cannot be worn, it often

is possible to perform repairs under local anesthesia; xylocaine is an excellent agent in such a case.

The place of operation in the correction of stress incontinence has not been settled; numerous procedures have been devised and Kegel[4] has proposed exercises as an alternative method of dealing with this problem. This proposal is still being evaluated but information available to date suggests that exercises have a very definite place in the role of preventing the onset of these symptoms, treating mild to moderate degrees of it, and as a preparation for surgery. The decision for operation may often be wisely left to the patient, as she may be the only one who can decide whether her trouble is of sufficient severity to require surgical relief. When operation is contemplated, a vaginal repair should be attempted first and if this fails the various urethral suspension operations[5] may be tried.

The field of vaginal plastic repair constitutes an excellent test of a surgeon's training and skill, since it is necessary to tailor the procedure to the individual situation. A poorly executed repair may be worse than none. Abdominal uterine suspensions for the relief of prolapse and other vaginal relaxations, fortunately, are becoming rare, for they are inadequate and generally useless procedures. The Watkins interposition operation also is becoming less popular than formerly, since the later diagnosis and treatment of an intrauterine pathologic condition is considerably complicated when that operation has been employed.

SUMMARY

Symptoms of vaginal relaxation often can be relieved by vaginal plastic repair. In selecting patients for operation, symptoms, pelvic findings, physical condition, and personality must all receive consideration. Since the operation most often is elective, the patient should be apprised of her condition and be guided by the physician in making the decision for or against surgical relief. Vaginal plastic operations are contraindicated in women who have no symptoms of vaginal relaxation.

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THROMBOANGIITIS OBLITERANS: OCCURRENCE IN A BROTHER AND A SISTER

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THROMBOANGIITIS obliterans has been observed in sisters,[1-8] in brothers,[9,10] and in father and son,[11] but to our knowledge this report is the first of its occurrence in brother and sister. In early adult life, both had symptoms and signs of peripheral vascular disease. The clinical findings were typical of thromboangiitis obliterans.

CASE REPORTS

Case 1. A 30 year old man of Bohemian descent was examined in April 1942 because of a three-year history of recurrent ulcer of the toe and intermittent claudication at the level of the calf. Examination revealed color and temperature changes in both feet. There was an ulcer on the great toe of the right foot. The pulses of the feet were absent bilaterally. There was no evidence of diabetes. The patient had been smoking approximately 30 cigarettes per day for 12 years. He stopped smoking, was placed on conservative management, and obtained relief of symptoms.

Following this observation, the patient was seen on five separate occasions over a 12-year period because of exacerbations of the vascular disease. These are briefly outlined below. Each recurrence was preceded by a period of smoking, although he had been repeatedly warned not to smoke.

Twenty-one months after first examination (January 1944) the patient returned because of pain and swelling of the middle finger of the right hand. Oscillometric readings at the wrist level were reduced. A subungual abscess was incised and drained, and again the patient's symptoms subsided with conservative treatment.

He was next seen in December 1948, approximately six and a half years after the initial examination. He complained of a severe retrosternal pain. The electrocardiogram showed changes consistent with acute posterior myocardial infarction. The suspected cause of the infarction was thromboangiitis obliterans.

In March 1950, nine years after initial examination, he returned because of pain and an ulcer in the great toe of the left foot. Treatment with debridement, caudal blocks, and antibiotics relieved the symptoms, but they recurred in October of 1950. A left lumbar sympathectomy and sequestrectomy of the great toe of the left foot were performed in January 1951, and the distal phalanx of the great toe of the right foot was removed in March 1951.

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He was not seen again until June 1953, approximately 11 years after his initial visit, when he returned because of pain and a recurrence of the ulcer in the great toe of the left foot of one week's duration. At this time he could walk one block without leg pain. When exposed to cold, the fifth digit of the right hand turned pale, and when he walked rapidly, retrosternal pain developed which was relieved by rest and nitroglycerine. He had been smoking 20 cigarettes per day.

Case 2. In May 1954, a 33 year old housewife, the sister of the patient discussed in case 1, was first examined because the great toe of the left foot had become infected as a result of an ingrown toenail. The infection had begun six months previously, and had not responded well to local therapy. The infection continued to drain seropurulent material.

She had no prior history of foot ulcers, diabetes, or varicose veins. During the past two years she had noted that exposure to cold caused the fingers to blanch and to become numb.

She had smoked 20 cigarettes per day since the age of 25 years.

Physical examination revealed a dusky cyanosis of the fingers and toes. There was an area of gangrene on the great toe of the left foot (fig. 1), and an area of discoloration and desquamation of the left heel, which appeared to be an incipient ulcer. The posterior tibial and dorsalis pedis pulses were absent bilaterally. Oscillometric readings were 0 in both feet, and ¾ in the right and ½ in the left ankle. The Allen test revealed obstruction of the right ulnar artery.

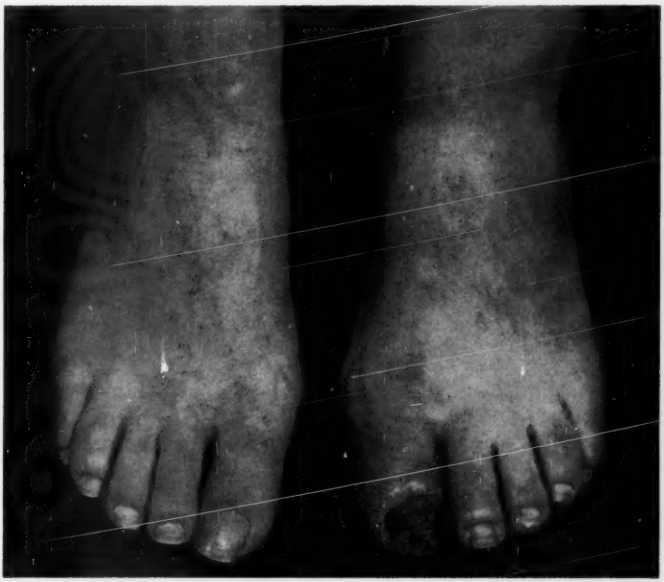

Fig. 1. (Case 2) Note area of gangrene involving left great toe.

The patient was admitted to the hospital where she was treated with left lumbar sympathetic blocks, antibiotics, and local foot care. She stopped smoking completely.

Her condition was much improved after three weeks of treatment. She was discharged and conservative treatment was continued at home. The patient was last seen in September 1954; at that time, although the pulses were not palpable in the left foot, it was warm and the color had greatly improved.

COMMENT

We believe that the diagnosis of thromboangiitis obliterans is substantiated in each of our cases by the history and the clinical findings, although confirmation by pathologic examination is not available.

A diagnosis of Raynaud's disease must be considered in young adults, especially women, who have symptoms of peripheral vascular disease. In both of our cases a diagnosis of Raynaud's disease was excluded because of the absence of major arterial pulsations. The possibility of arteriosclerosis obliterans was eliminated because of the young age of both patients; in addition, examination of the fundi revealed no signs of arteriosclerosis, and roentgenograms of the lower extremities demonstrated no evidence of arterial calcification.

The bases of the diagnosis of thromboangiitis obliterans in each patient were: young age; history of having been a heavy smoker for many years; absence of major pulsations including those of the upper as well as of the lower extremities; temperature and color changes; and painful ulcers. In addition, the marked improvement in symptoms in each patient when smoking was stopped further substantiated the diagnosis, since this manifestation is most frequently encountered in thromboangiitis obliterans.

CONCLUSION

The occurrence of thromboangiitis obliterans in a brother and a sister supports the belief that heredity plays a role in the susceptibility of the arteries to this disease.

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HEADACHE AND PEPTIC ULCER

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HEADACHE is one of the most common symptoms of an underlying nervous tension state. For all practical purposes, chronic or recurrent headache is due to one of two mechanisms: (1) excessive dilatation of extracranial arteries, or (2) excessive tension in the muscles of the head and neck. In the past, many organic causes have been listed and the medical literature is filled with reports stressing the frequency of head pain due to disease processes in the eyes, sinuses, nasal structures, and teeth. Head trauma and injuries to the neck have been incriminated as frequent causes of headache. Even such conditions as glandular disease, gastrointestinal disorders, and pelvic disease have been listed as common causes of headache. The truth is that all such "organic" diseases have very little to do with the production of headache. The noxious stimuli are almost always cerebral in origin and produce the excessive vasodilatation or increased muscle tension resulting in pain by humoral or nervous mechanisms not yet well understood. Headache is truly a disease of civilization and stress.

Peptic ulcer is another well-recognized disease of civilization. Although it is commonly regarded as a specific disease, it might be more accurately thought of as another manifestation of nervous tension state. It has often been said that it is relatively easy to heal an ulcer, but most difficult to prevent its recurrence. When medical treatment fails, the problem can often be handled quite satisfactorily by surgical procedures designed to inhibit gastric hypersecretion. This can be accomplished either by interruption of vagal stimulation from the higher centers (vagotomy) or by removing the source of hormonal stimulation (gastric resection).[1]

Why is it then, that a brilliant surgical result insofar as cure of the ulcer is concerned, fails to produce a healthy patient in many instances? In a considerable number of cases, even the most critical observer must admit that the stomach trouble has been relieved—but the patient has new symptoms related to the tension state that has not been influenced by the surgeon's knife. Headache, fatigue, and depression sometimes occur after cure of the peptic ulcer. It is only natural that in follow-up reports after surgical procedures designed for the relief of ulcer, attention is focused on what happens to the ulcer, rather than on what happens to the patient.

It is the experience of every surgeon that some patients do not get well even when the ulcer is cured. In desperation, he then turns to his medical colleagues for help. It is not surprising that headache may be a bothersome symptom after the ulcer has been controlled. In the course of a year we have had the opportunity to see a number of patients who "refused to get well" after a very successful operation.

This report is concerned with seven patients who were subjected to vagotomy for peptic ulcer and in whom an excellent initial result was obtained. However, all of these patients returned with a complaint of headache.

CASE REPORTS

Case 1. A 62 year old man first seen in January 1951, with ulcer history of 31 years' duration. Gastroenterostomy had been performed in 1926. Since 1926, seven episodes of massive hemorrhage, four of them in the last one and a half years. Diagnosis of marginal ulcer made and vagotomy performed February 20, 1951. Excellent postoperative result.

Seen July 14, 1953 (17 months postoperatively), with chief complaint of headache. History of life-long periodic sick headache more severe during past year. Present headache two to three times weekly awakening him early in morning.

Diagnosis: Chronic nervous tension state. Extracranial vascular headache.

Case 2. A 31 year old woman first seen August 1946. Epigastric pain of six months' duration. Diagnosis of duodenal ulcer made. Next seen February 4, 1948, with history of three bouts of massive hemorrhage. Vagus resection and pyloroplasty performed February 11, 1948. Convalescence uneventful; follow-up revealed no further gastrointestinal trouble and patient very pleased with the results of operation.

June 1952, still free of gastrointestinal symptoms, but having severe headache. History of sick headache many years, but became worse during past year.

Diagnosis: Chronic nervous tension state. Extracranial vascular headache.

Case 3. A 26 year old man was first seen in January 1950. History indicated onset of ulcer symptoms in 1945, with massive hemorrhages in 1947, 1948, 1949. Vagotomy and gastroenterostomy performed January 31, 1950. Excellent result; no further ulcer trouble. Last seen February 1952, with chief complaint of headache. History of some headache since 1944 but much worse during past year.

Diagnosis: Chronic nervous tension state. Muscle tension headache.

Case 4. A 51 year old man first seen in July 1950. Three episodes of melena—1945, 1948, and July, 1950. Diagnosis of chronic duodenal ulcer and cholelithiasis. In October 1950, vagotomy, posterior gastrojejunostomy and cholecystectomy performed. No symptoms until August 1951, then developed irritable colon. In January 1952, chief complaint related to headache of 12 years' duration, but more severe during past year.

Diagnosis: Chronic nervous tension state. Muscle tension headache.

Case 5. A 32 year old man first seen in 1943, with periodic epigastric distress of 15 years' duration and occasional headache. Diagnosis of chronic duodenal ulcer and irritable bowel. In 1944 gastrointestinal symptoms improved but chief complaint of nervousness and weak spells. Diagnosis of neurocirculatory asthenia. Seen in October 1951, with chief complaint of headache coming on after vagotomy for duodenal ulcer performed elsewhere, March 1949. Patient blamed headache on vagotomy.

Diagnosis: Chronic anxiety tension state. Muscle tension headache.

Case 6. A 45 year old man first seen February 1949, with ulcer history of 12 years' duration. Periodic headache as long as he could remember, but constant the past year.

Vagus resection and pyloroplasty performed April 1949. In June 1949, no symptoms related to gastrointestinal tract but headache worse. In May 1951, complete examination because of epigastric burning and headache. Diagnosis of chronic nervous tension state. In August 1951, hospitalized for bacterial pneumonia; no headache during this period.

July 1952, readmitted to hospital with evidence of duodenal obstruction. Gastroenterostomy performed, obstruction found to be due to adhesions; no evidence of ulcer. Headache disappeared during hospitalization. Last seen January 1954, with recent fracture of right hip and peroneal palsy. No gastrointestinal symptoms; no headache.

Diagnosis: Chronic nervous tension state. Muscle tension headache.

Case 7. A 44 year old man first seen in August 1949. Ulcer symptoms since 1939; gastric resection in November 1946. Relief for seven months, then return of symptoms. Diagnosis of marginal ulcer made in August 1949; vagotomy performed September 1949. Three-fourths of stomach still present; marginal ulcer 2 cm. in diameter. October 1949, listed as "perfect result" from standpoint of gastrointestinal symptoms. However, complained of occipital headache, worse since surgery. Diagnosis of chronic nervous tension state with muscle tension headache.

In March 1951, no mention of headache but chief complaint of tiredness and weakness.

Last seen October 1951 (two years postoperatively); very little trouble with stomach, but symptoms everywhere else. Still having headache.

Diagnosis: Severe anxiety neurosis.

COMMENT

The case histories have been condensed, and only the bare facts stated. However, each of the patients had considerable difficulty with life adjustment, and the complete history disclosed many tensions, frustrations, and personality difficulties. The disease was not primarily peptic ulcer; the ulcer was only a manifestation of the underlying disorder and when it was removed, another symptom took its place.

Menninger[2] stated this concept quite clearly when he wrote that neither the peptic ulcer nor the colitis and associated depressive or paranoid states are in themselves the disease; the disease is a defective total life adjustment. Brosin[3] points out the concept of a psychosomatic affliction as a partial manifestation of maladaptation to life stress by the human organism. This mechanism often permits the person to carry on his job and domestic duties in conventional ways. As an example, he listed the frequency with which chronic alcoholics in "dry" periods show depressive states. It is not infrequent that a chronic alcoholic who has ceased drinking because of participation in Alcoholics Anonymous or by some other means, suffers from recurrent headache.[4]

It will be noted that of the seven patients listed, five suffered from muscle tension headache and only two from the generally more common extracranial vascular headache. It is of interest, and probably of significance, that all of the patients had some trouble with headache prior to surgery; the headache became *worse* after the ulcer symptoms were controlled. It is not to be construed that vagotomy per se has anything to do with the production of headache; although no figures are available, it is our opinion that such a problem would be as frequently encountered after gastric resection for peptic ulcer, or after resection of the colon for ulcerative colitis. The disease has not been removed and the individual requires another symptom to facilitate adjustment in a socially acceptable manner.

Unfortunately, there are those who still demand an "organic" explanation for headache and find it difficult to believe that severe pain can be produced by "functional" conditions. Fortunately, the terms "functional" and "organic" are rapidly losing their strict meanings, for such a division can serve no useful purpose. Headache produced by sustained contractions of the scalp and neck muscles is usually emotionally induced, though it need not be. This type of headache has been blamed on osteoarthritis, errors of curvature of the cervical spine, posture, and a variety of other causes. Since it is observed rather commonly in conjunction with duodenal ulcer, and in a relatively young age group, the proponents of organic cause would be hard-put to explain why people with duodenal ulcer should develop arthritis or show errors in cervical curvature more commonly than individuals in the general population. Or why they should have more frequent neck trauma, or more "neuralgia."

The surgeon should not be criticized for using any means at his disposal to try to effect a cure of peptic ulcer, nor should he be too concerned when a brilliant result is marred by the development of some other symptom—especially headache. After all, even in the patients reported here, a serious painful disorder has been converted to a benign painful disorder—and that represents a considerable gain. Headache is the social excuse par excellence and has been for centuries; it is a very helpful device. Perhaps the overenthusiastic clinician should be warned against trying to take away this helpful prop lest the whole personality crumble in a fit of depression or psychotic episode.

SUMMARY

1. Seven patients with peptic ulcer who were subjected to vagotomies and in whom excellent results were obtained as measured by disappearance of gastrointestinal symptoms and healing of the ulcers, were later seen with chief complaints of headache.

2. The headaches could be classified as being due to sustained muscle contractions of the head and neck in five cases, and extracranial vascular in type in two cases.

3. The basic disease in these patients is neither peptic ulcer nor headache; it is a defect in total life adjustment.

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ERRATUM

In the April 1954 QUARTERLY, on page 112, paragraph 2, line 4, the dosage should read: *1.0* mg.

RECENT PUBLICATIONS BY MEMBERS OF THE STAFF

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TAYLOR, R. D., CORCORAN, A. C., DUSTAN, H. P. and PAGE, I. H.: Further evaluation of hydralazine in treatment of hypertensive disease. A.M.A. Arch. Int. Med. **93**: 705-712 (May) 1954.

ANNOUNCEMENT

Physician-in-Chief Pro Tempore

Dr. Samuel A. Levine, clinical professor of medicine, Harvard Medical School, and physician at the Peter Bent Brigham Hospital, Boston, will be the fourth annual Physician-in-Chief pro tempore on December 16, 17, and 18, 1954. During his tenure, Dr. Levine will devote his entire time to the teaching program of the Fellows in Medicine. A schedule of daily clinics, lectures, and seminars has been arranged. Members of the medical profession are cordially invited to attend.

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

announces a postgraduate course on

DISEASES OF THE CHEST

October 27 and 28, 1954

Sponsored by

CLEVELAND SOCIETY FOR DISEASES OF THE CHEST

and

AMERICAN COLLEGE OF CHEST PHYSICIANS

Tentative Program

Wednesday, October 27, 1954

8:00- 9:00 a.m. . Registration
Morning Session . . . . . H. S. VAN ORDSTRAND, M.D., Presiding

9:00- 9:05 a.m. . Opening Remarks . . . . . F. A. LEFEVRE, M.D.

9:05- 9:25 a.m. . Present Status of Antimicrobial Treatment . . HAROLD CURTIS, M.D. *

9:25- 9:45 a.m. . Pathology as Affected by Antimicrobial Therapy in Tuberculosis . . . . . THOMAS KINNEY, M.D. *

9:45-10:05 a.m. . Surgical Trends in Tuberculosis . . . HARVEY MENDELSOHN, M.D. *

10:05-10:25 a.m. . Immunization with BCG . . . . . M. M. PERLICH, M.D. *

10:25-10:45 a.m. . Trends in Tuberculosis Control . . . . . J. B. STOCKLEN, M.D. *

10:45-11:00 a.m. . Intermission

11:00-11:30 a.m. . Diagnosis and Antibiotic Therapy of the Pneumonias . . . . . THEODORE WOODWARD, M.D. *

11:30-11:50 a.m. . Mucoviscidosis . . . . . R. D. MERCER, M.D.

11:50-12:10 p.m. . Diagnostic Value of Kveim Test in Sarcoidosis . J. R. HASERICK, M.D.

12:30- 2:00 p.m. . Luncheon—Courtesy Bunts Institute
Afternoon Session

2:00- 3:30 p.m. . Panel Discussion—
Emphysema . . . . . H. S. VAN ORDSTRAND, M.D., Moderator
GEORGE WRIGHT, M.D. *
R. N. WESTCOTT, M.D.
DAVID GILLESPIE, M.D. *

3:30- 3:45 p.m. . Intermission

3:45- 5:00 p.m. . Panel Discussion—
Pneumoconioses . . . . . RAYMOND MCKAY, M.D., Moderator *
SIDNEY WOLPAW, M.D. *
H. S. VAN ORDSTRAND, M.D.
GEORGE WRIGHT, M.D. *

Thursday, October 28, 1954

	Morning Session	F. A. LeFevre, M.D., Presiding
9:00- 9:20 a.m.	Surgery of Septal Defects	Earl B. Kay, M.D.*
9:20- 9:40 a.m.	Surgery of Congenital Heart Disease	D. B. Effler, M.D.
9:40-10:00 a.m.	The Experimental and Clinical Use of the Heart-Lung Apparatus	George Clowes, M.D.*
10:00-10:20 a.m.	Pericardial Biopsy	W. L. Proudfit, M.D.
10:20-10:40 a.m.	Cardiac Arrest	C. E. Wasmuth, M.D.
10:40-11:00 a.m.	Intermission	
11:00-12:00 noon	Panel Discussion— Surgery in Mitral Stenosis	A. C. Ernstene, M.D., Moderator F. M. Sones, Jr., M.D. Salvatore Sancetta, M.D.* Henry Zimmerman, M.D.*
12:30- 2:00 p.m.	Luncheon—Courtesy Bunts Institute	
	Afternoon Session	D. B. Effler, M.D., Presiding
2:00- 2:15 p.m.	Cytologic Studies in Lung Cancer	L. J. McCormack, M.D.
2:15- 2:45 p.m.	Diagnosis and Treatment of Bronchogenic Carcinoma	Walker Munz, M.D.*
2:45- 3:15 p.m.	Management of Mediastinal Tumors	Fred Cross, M.D.*
3:15- 3:30 p.m.	Intermission	
3:30- 3:50 p.m.	Coin Lesions	L. K. Groves, M.D.
3:50- 4:20 p.m.	Lung Biopsy in Diffuse Lung Lesions	H. S. Van Ordstrand, M.D.
4:20- 4:45 p.m.	Middle Lobe Syndrome	D. B. Effler, M.D.

* *Guest Speaker.*

REGISTRATION BLANK

Educational Secretary
The Frank E. Bunts Educational Institute
Cleveland Clinic
East 93rd Street and Euclid Avenue
Cleveland 6, Ohio

Please register me for the course on "Diseases of the Chest" to be given October 27 and 28, 1954. (Registration Fee is $15.00, except for interns and residents, and members of the Armed Forces in uniform, who will be admitted free.)

I am enclosing check for $5.00 and the remainder will be paid on registration, October 27.

Checks should be made payable to the Frank E. Bunts Educational Institute.

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Medical School and
Date of Graduation . . . . . .

This course is open only to graduates of approved medical schools.

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

announces a postgraduate continuation course
November 10 and 11, 1954

ANNUAL REVIEW COURSE IN GENERAL SURGERY

Tentative Program

Wednesday, November 10, 1954

8:00- 9:00 a.m. . Registration

9:00-12:30 p.m. . Morning Session . . . . . R. S. DINSMORE, M.D., Presiding
Opening Remarks . . . . . R. S. DINSMORE, M.D.
Diseases of the Breast . . . . . R. S. DINSMORE, M.D.
R. K. GILCHRIST, M.D.*
R. A. HAYS, M.D.
D. M. GLOVER, M.D.*
A. H. ROBNETT, M.D.
Advances in Surgery of the Colon . . R. B. TURNBULL, JR., M.D.
R. K. GILCHRIST, M.D.*
A. H. ROBNETT, M.D.
Surgery of the Heart and Lungs . . . . .D. B. EFFLER, M.D.
L. K. GROVES, M.D.
H. S. VAN ORDSTRAND, M.D.
A. C. ERNSTENE, M.D.

12:30- 2-00 p.m. . Luncheon—Courtesy Bunts Institute

2:00- 5:00 p.m. . Afternoon Session . . . . . GEORGE CRILE, JR., M.D., Presiding
Diseases of the Pancreas . . . . . GEORGE CRILE, JR., M.D.
R. K. GILCHRIST, M.D.*
E. N. COLLINS, M.D.
S. O. HOERR, M.D.
Surgery of the Stomach and Duodenum . . . . S. O. HOERR, M.D.
R. K. GILCHRIST, M.D.*
C. H. BROWN, M.D.
C. R. HUGHES, M.D.

Thursday, November 11, 1954

9:00-12:30 p.m. . Morning Session . . . . . S. O. HOERR, M.D., Presiding
Diseases of the Thyroid . . . . . J. B. HAZARD, M.D.
R. S. DINSMORE, M.D.
GEORGE CRILE, JR., M.D.
E. P. MCCULLAGH, M.D.
Advances in Treatment of Peripheral Vascular Disease . . . . .
F. A. LEFEVRE, M.D.
A. W. HUMPHRIES, M.D.
A. H. ROBNETT, M.D.
J. C. ROOT, M.D.
F. A. SIMEONE, M.D.*

12:30- 2:00 p.m. . Luncheon—Courtesy Bunts Institute

2:00- 5:00 p.m. . Afternoon Session . . . . . R. B. TURNBULL, JR., M.D., Presiding

Developments in the Surgical Specialties

Urology . . . . . C. C. HIGGINS, M.D.
Orthopedic Surgery . . . . . J. I. KENDRICK, M.D.
Ophthalmology . . . . . R. J. KENNEDY, M.D.
Otolaryngology . . . . . H. E. HARRIS, M.D.
Head and Neck Cancer . . . . . ROBIN ANDERSON, M.D.
Neurosurgery . . . . . W. J. GARDNER, M.D.
Gynecology . . . . . J. S. KRIEGER, M.D.

* *Guest Speaker.*

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Please register me for the "Annual Review Course in General Surgery" to be given November 10 and 11, 1954. (Registration Fee is $15.00, except for interns and residents, and members of the Armed Forces in uniform, who will be admitted free.)

I am enclosing check for $5.00 and the remainder will be paid on registration, November 10.

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INDEX

CLEVELAND CLINIC QUARTERLY—Volume 21—1954

AUTHOR INDEX

Anderson, Robin: Repair of cleft lip, 180

Battle, J. D., Jr.: *see* Leiser, A. E.
Belaval, G. S. and Schneider, R. W.: Fibrous dysplasia of bone, 158
Biddlestone, W. R. and LeFevre, F. A.: Thromboangiitis obliterans: occurrence in brother and sister, 226
Brown, C. H. and Sims, J. R., Jr.: Regional enteritis involving duodenum: report of two cases, 95

Cassidy, C. E. and Karnosh, L. J.: Bell's palsy treated with cortisone: review of literature and report of cases, 176
Crile, George, Jr.: Errors in surgery of biliary tract, 90
—: *see* Hoerr, S. O.

deWolfe, V. G.: *see* Humphries, A. W.
Dickson, J. A.: *see* Patch, D. W.

Effler, D. B., Groves, L. K. and Sones, F. M., Jr.: Surgery for mitral stenosis. Part II. Mortality in mitral commissurotomy, 103
—, and Sones, F. M., Jr.: Surgery of aortic arch anomalies, 14
—: *see* Groves, L. K.
Engel, W. J.: Hyaluronidase as aid to correction of paraphimosis: report of case, 24

Fisher, E. R. and Whitman, John: Whipple's disease: report of case apparently cured and discussion of the histochemical features, 213

Glasser, Otto: *see* Kennedy, R. J.
Greenwald, C. M. and Whitsett, C. C.: Roentgenographic diagnosis of acoustic nerve tumor, 40
Groves, L. K., Effler, D. B. and Sones, F. M., Jr.: Controlled hypotension in surgical treatment of certain cases of patent ductus arteriosus: report of 4 cases, 169
—: *see* Effler, D. B.

Hale, D. E.: *see* Wasmuth, C. E.
Haserick, J. R.: *see* Rogers, F. J.
—: *see* Skirpan, Philip
Hoerr, S. O.: Cancer of stomach, 205
—, and Crile, George, Jr.: Which operation for chronic duodenal ulcer? 3
Humphries, A. W., LeFevre, F. A. and deWolfe, V. G.: Surgical treatment of arteriosclerosis obliterans: preliminary report, 197

Karnosh, L. J.: *see* Cassidy, C. E.
Kazdan, Philip: *see* Kennedy, R. J.
Kennedy, R. J., Glasser, Otto and Kazdan, Philip: Use of radioactive phosphorus in detection of intraocular tumors, 133
Kolff, W. J. and Leonards, J. R.: Reduction of otherwise intractable edema by dialysis or filtration, 61
Krieger, J. S.: Surgical approach to cervical carcinoma, 27
—: Surgical correction of vaginal relaxation, 222

LeFevre, F. A.: *see* Biddlestone, W. R.
—: *see* Humphries, A. W.
Leiser, A. E. and Battle, J. D., Jr.: Gaucher's disease: clinical features and indications for splenectomy, 6
Leonards, J. R.: *see* Kolff, W. J.
Lovshin, L. L.: Headache and peptic ulcer, 230

McCullagh, E. P., Skillern, P. G. and Schaffenburg, C. A.: Use of cortisone in treatment of panhypopituitarism due to postpartum necrosis of pituitary (Sheehan's syndrome), 31

Patch, D. W., Phalen, G. S. and Dickson, J. A.: Osteoid osteoma, 123
Phalen, G. S.: *see* Patch, D. W.
Proudfit, W. L.: Review article: Quinidine in treatment of auricular arrhythmias, 110; (*see* correction, 234)

Rogers, F. J. and Haserick, J. R.: Value of Kveim test as diagnostic measure in sarcoidosis: preliminary report, 79
Roncagli, Gaetano: *see* Wasmuth, C. E.

Schaffenburg, C. A.: *see* McCullagh, E. P.
Schneider, R. W.: *see* Belaval, G. S.
Sims, J. R., Jr.: *see* Brown, C. H.
Skillern, P. G.: *see* McCullagh, E. P.
Skirpan, Philip and Haserick, J. R.: Keratoacanthoma: histopathologic criteria for diagnosis, 153
Sones, F. M., Jr.: *see* Effler, D. B.
—: *see* Groves, L. K.

Van Ommen, R. A.: Clinical manifestations of idiopathic hypoparathyroidism: report of case, 72

Wasmuth, C. E. and Hale, D. E.: Changing concepts of anesthesia depth, 46
—, and Roncagli, Gaetano: Management of continuous spinal anesthesia for geriatric surgery, 141
Whitman, John: *see* Fisher, E. R.
Whitsett, C. C.: *see* Greenwald, C. M.

SUBJECT INDEX

Entries set in *italics* refer to specific titles of articles

Anesthesia
  continuous spinal, for geriatric surgery, 141
  depth of, changing concepts of, 46
Announcement, 237
Anomalies, aortic arch, surgery of, 14
Arrhythmias, auricular, quinidine in treatment of, 110
Arteriosclerosis obliterans, surgical treatment of, 197

Bell's palsy treated with cortisone: review of literature and report of cases, 176
Bunts Institute Courses, tentative programs
  Basic science
    clinical application of basic sciences, 56
    review course in general surgery, 57
  Postgraduate
    current therapy in pediatric practice, 189
    diseases of chest, 191, 238
    review course in general surgery, 240

Cancer of stomach, 205
Carcinoma, cervical, surgical approach to, 27
Cervix, carcinoma of, surgical approach to, 27
Changing concepts of anesthesia depth, 46
Clinical manifestations of idiopathic hypoparathyroidism: report of case, 72
Commissurotomy, mitral, mortality in, 103
Controlled hypotension in surgical treatment of certain cases of patent ductus arteriosus: report of 4 cases, 169
Cortisone
  in treatment of Bell's palsy, 176
  use of in treatment of panhypopituitarism due to postpartum necrosis of pituitary, 31

Dialysis, reduction of edema by, 61
Ductus arteriosus, patent, controlled hypotension in surgical treatment of, 169
Duodenum
  involvement of, in regional enteritis, 95
  ulcer of, which operation for, 3
Dysplasia, fibrous, of bone, 158

Edema, otherwise intractable, reduction of, by dialysis or filtration, 61
Enteritis, regional, the duodenum involved in, 95
Erratum, 234
Errors in surgery of biliary tract, 90
Eyes
  intraocular tumors, use of radioactive phosphorus in detection of, 133

Fibrous dysplasia of bone, 158
Filtration, reduction of edema by, 61

Gaucher's disease: clinical features and indications for splenectomy, 6
Geriatric surgery, continuous spinal anesthesia for, 141

Headache and peptic ulcer, 230
Hyaluronidase as aid to correction of paraphimosis: report of case, 24
Hypoparathyroidism, idiopathic, clinical manifestations of, 72
Hypotension, controlled, in surgical treatment of patent ductus arteriosus, 169

Keratoacanthoma: histopathologic criteria for diagnosis, 153
Kveim test, value of, as diagnostic measure in sarcoidosis, 79

Lip, cleft, repair of, 180
Lipodystrophy, intestinal, report of case apparently cured and discussion of histochemical features of, 213

Management of continuous spinal anesthesia for geriatric surgery, 141
Mitral valve
commissurotomy, mortality in, 103
stenosis, surgery for, 103

Nerve, acoustic, tumor of, roentgenographic diagnosis of, 40

Osteoid osteoma, 123
Osteoma, osteoid, 123

Palsy, Bell's, cortisone in treatment of, 176
Panhypopituitarism, due to postpartum necrosis of pituitary, use of cortisone in treatment of, 31
Paraphimosis, hyaluronidase as aid to correction of, 24
Phosphorus, radioactive, use of in detection of intraocular tumors, 133
Pituitary, postpartum necrosis of, panhypopituitarism due to, use of cortisone in treatment of, 31
Plastic surgery, 180
Publications by staff, listings of, 54, 117, 187, 235

Quinidine, treatment of auricular arrhythmias with, 110

Radioactive phosphorus, use of in detection of intraocular tumors, 133
Reduction of otherwise intractable edema by dialysis or filtration, 61
Regional enteritis involving the duodenum: report of 2 cases, 95
Relaxation, vaginal, surgical correction of, 222
Repair of cleft lip, 180
Review article: Quinidine in treatment of auricular arrhythmias, 110 (*see* correction, 234)
Roentgenographic diagnosis of acoustic nerve tumor, 40

Sarcoidosis, value of Kveim test as diagnostic measure in, 79
Sheehan's syndrome, panhypopituitarism due to, use of cortisone in treatment of, 31
Splenectomy, clinical features and indications for, in Gaucher's disease, 6
Stomach, cancer of, 205
Surgery for mitral stenosis. II. Mortality in mitral commissurotomy, 103
Surgery of aortic arch anomalies, 14
Surgical approach to cervical carcinoma, 27
Surgical correction of vaginal relaxation, 222
Surgical treatment of arteriosclerosis obliterans: preliminary report, 197

Thromboangiitis obliterans: occurrence in brother and sister, 226
Tract, biliary, errors in surgery of, 90
Tumor
acoustic nerve, roentgenographic diagnosis of, 40
intraocular, use of radioactive phosphorus in detection of, 133

Ulcer
duodenal, which operation for, 3
peptic, headache and, 230
Use of cortisone in treatment of panhypopituitarism due to postpartum necrosis of pituitary (Sheehan's syndrome), 31
Use of radioactive phosphorus in detection of intraocular tumors, 133

Vagina, relaxation of, surgical correction of, 222
Value of Kveim test as diagnostic measure in sarcoidosis: preliminary report, 79

Which operation for chronic duodenal ulcer? 3
Whipple's disease: report of case apparently cured and discussion of histochemical features, 213